Medical Lib.
OCT 18 1926

VOL. CLXXII, No. 4 OCTOBER, 1926 No. 655

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

E. B. KRUMBHAAR, M.D., EDITOR
RICHARD A. KERN, M.D., ASSISTANT EDITOR

ESTABLISHED 1820

PROBLEMS IN RENAL PATHOLOGY. By ELI MOSCHCOWITZ, M.D. 469

EXPERIMENTAL NEPHRITIS PRODUCED BY IRRADIATION. By F. W. HARTMAN, M.D., ADOLPH BOLLIGER, PH.D., and H. P. DOUB, M.D. 487

CONSIDERATIONS OF THE PROBLEM OF BLOOD CLOTTING. By C. A. MILLS . . 501

THE INFLUENCE OF VARIOUS FACTORS UPON THE HEMAGGLUTINATION OF RED BLOOD CORPUSCLES. By CHARLES C. HIGGINS, M.D. 510

LEUKEMOID BLOOD PICTURES IN VARIOUS CLINICAL CONDITIONS. By E. B. KRUMBHAAR, M.D. PH.D. 519

THE OCCURRENCE OF ANEMIA IN FOUR GENERATIONS. By W. W. G. MACLACHLAN, M.D., and FLORENCE M. KLINE, M.D. 533

PERIODIC VARIABILITY OF SOME FORMS OF ARTERIAL HYPERTENSION. By LOUIS H. SIGLER, M.D. 543

HEMOGLOBIN ESTIMATES IN PREGNANCY. By WILLIAM KERWIN, M.D., F.A.C.S., and LISLÉ L. COLLINS, M.D. 548

VARICOSE ULCER: MECHANISM OF ITS CAUSATION AND CURE, WITH NOTES ON THE ASSOCIATED PAIN AND PUPIL INEQUALITY. By JOSEPH BYRNE, A.M., M.D., LL.D. 553

HUMAN GASTRIC RESPONSE TO MEAT AND YEAST EXTRACTS By LOUIS M. GOMPERTZ, M.D., and WILLIAM COHEN, M.D. 565

CHOLECYSTITIS ASSOCIATED WITH SITUS TRANSVERSUS. REPORT OF A CASE AND A BRIEF REVIEW OF THOSE FOUND IN MEDICAL LITERATURE. By R. B. BETTMAN, M.D., F.A.C.S., and HERBERT F. BINSWANGER, M.D. 570

HYPOGLYCEMIC COMA DUE TO REPEATED INSULIN OVERDOSAGE. By ELMER L. SEVRINGHAUS, M.D. 573

RUPTURED GRAAFIAN FOLLICLE OR CORPUS LUTEUM CYST SIMULATING ACUTE APPENDICITIS. REVIEW OF CASES IN NEW YORK HOSPITAL SINCE 1914. By ELIZABETH BRAKELEY, PH.D., and CHARLES E. FARR, M.D. 580

MYXEDEMATOUS ASCITES REMOVED BY THYROID EXTRACT. By HAROLD E. MARSH, M.D. 585

THE TREATMENT OF HAY FEVER WITH EPHEDRIN. PRELIMINARY REPORT. By FRED W. GAARDE, M.D., and CHARLES K. MAYTUM, M.D. 588

DUODENAL DIVERTICULUM. WITH REPORT OF A CASE ASSOCIATED WITH DEFINITE SYMPTOMS. By R. H. KAMPMEIER, B.A., M.D. 590

INDEX TO ADVERTISERS . . . . . ADV. PAGE 42

Contents continued on page x

OWNERS AND PUBLISHERS
Philadelphia LEA & FEBIGER New York

COPYRIGHT, 1926, BY LEA & FEBIGER. ALL RIGHTS RESERVED. ENTERED AT THE POST-OFFICE AT PHILADELPHIA AS SECOND-CLASS MATTER

PUBLISHED MONTHLY. SUBSCRIPTION, SIX DOLLARS A YEAR, POSTPAID

INFANT DIET **MEAD'S** MATERIALS

What is Mead's Standardized Cod Liver Oil?

Mead's Standardized Cod Liver Oil is accepted as a criterion of excellence not only by physicians, but also by other pharmaceutical manufacturers. *It is an established measure of quality regulated by a standard.*

Mead's is the first commercial oil tested to a standard of antirachitic potency. This standard was established after four years of investigation and testing of cod liver oils secured at the site of production in different countries of the world. Biological assay proved the *Newfoundland* oils to be most uniform in the active principle—the antirachitic factor or Vitamin D. Smaller doses of Newfoundland oil healed experimental rickets in animals in a shorter period of time than oils from other countries. Newfoundland oils also produced more prompt clinical evidence of healing of rickets in bones of infants as seen by the radiograph.

Standardization of Mead's oil means:

The ownership of 40 rendering plants in Newfoundland.

The rendering of oil from *strictly fresh cod livers* within four hours after the fish are caught.

A standard, uniform method of rendering each batch of oil.

The careful removal of stearine —the non-antirachitic factor.

The numbering, registering, and biological assay of each batch of oil.

The selection for the physician of batches of oil that meet the standard for biological assay, and the disposal of oil under the standard to tanneries and soap manufacturers.

That the standard oils must show definite healing in severe rickets in experimental animals in 5 days when one part oil to 400 parts diet is fed to the rat. Some of our oils test even higher than this.

Mead's Standardized Cod Liver Oil is a trustworthy product, and if given to infants during the first two years of life, will greatly reduce rickets. The physician is gratified with the results obtained, and protects the baby in his care when he specifies MEAD'S.

Samples and scientific literature sent cheerfully on request.

MEAD JOHNSON & COMPANY, Evansville, Indiana, U. S. A

Manufacturers of Infant Diet Materials Exclusively

THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

OCTOBER, 1926

ORIGINAL ARTICLES.

PROBLEMS IN RENAL PATHOLOGY.*

By Eli Moschcowitz, M.D.,

ASSOCIATE PHYSICIAN IN MT. SINAI HOSPITAL, NEW YORK.

Classification. Let us analyze some of the reasons for the confusion in current classifications of the nephritides.

1. The classification may be based upon *etiology*. This is obviously fallacious because: (*a*) We do not know the cause of many of the nephropathies; (*b*) the same factor or agent (for example, the streptococcus) may result in a variety of lesions; (*c*) the same lesion (for example, an acute glomerulonephritis) can be produced by different causes.

2. The classification may be *clinical*. Such classifications fail for the following reasons: (*a*) The clinical manifestations of nephropathies overlap. Almost any symptom or sign may be produced by a number of widely different disorders so that a completely identical clinical picture may be associated with two entirely separate lesions. (*b*) The clinical manifestations of almost any nephropathy are usually never complete in the sense of an end result. Most nephropathies are characterized by stages, and the final stage is often entirely different from the initial one. This change is usually consequent upon the natural history of the disease, but often upon the result of an extrarenal complication as well. One reason that we know so little of many of the chronic diseases is because we are not aware of what has gone before. We

* Read by Invitation at the University of Michigan, Ann Arbor, Michigan, April 8, 1926.

always see the terminal phases, very often the intermediate phases, rarely (because they are practically symptomless) the initial phases, and most rarely of all, are we sufficiently fortunate to observe a slowly progressing malady from the beginning to the end.* It is apparent, therefore, that a classification attended by protean clinical characteristics is bound to be hazardous. (*c*) A large group of the nephropathies, and I refer especially to the chronic nephritides, are not in the strict sense diseases of the kidney. The dominant symptoms and signs, especially in the middle and terminal phases are the result of extrarenal lesions, notably in the vascular system. In fact, it is sometimes difficult to determine whether the malady is primarily cardiac or renal. Here again, diagnosis depends upon our knowledge of incipient disease.

3. The classification may be based upon *morbid anatomy*. Such a classification would seem most desirable because it is the most logical. Current classifications based on pathology, however, vary widely for the following reasons: (*a*) Pathologists are by no means in accord as to terminology. Different synonyms are employed to indicate similar lesions. Furthermore, they are not even agreed in regard to the interpretation of the term "inflammation," so that a "nephritis" to some is not a "nephritis" to others. (*b*) Pathologists have even less opportunity than clinicians to witness the progression of a lesion from its inception. They only see the end result after the cessation of physiologic functions, and so have erroneously been led into the habit of interpreting the findings at autopsy as completed anatomic lesions. It need hardly be denied that a classification of the anatomic stages of a disease is decidedly fallacious. This fact alone should have made pathologists suspicious that they were not dealing with end results. There has hitherto been an uncritical interpretation of function in terms of morbid anatomy and *vice versa*. In the first place, we are still too largely under the traditional sway of the continental teaching that abnormal function must always be interpreted as secondary to an anatomic lesion. The process is often reversed and a renal lesion may sometimes be the result of an exaggerated normal function, namely, intravascular tension. This accounts for the many surprises found at postmortem in patients with nephropathies. Unfortunately, there is only a tenuous correlation between functional data and autopsy findings, and in a large group of nephropathies, one cannot predict the anatomic diagnosis. In other words, clinical nephritis and pathologic nephritis may be two entirely different things. This would have been recognized more widely had pathologists been clinicians, and clinicians pathologists. (*d*)

* I believe, for instance, that we shall gain better knowledge of the baffling group of hepato-lienal diseases, when we have observed a number of such cases from their very inception. This is essentially a problem within the province of the general practitioner.

There is utter disagreement in regard to the pathogenesis of nephropathies and this leads to a varying conception of the lesion. We are by no means in the position to know the origin and order of progression of the disease in the different components of the kidneys, whether the disease begins in the vessels, the parenchyma, the interstitium or simultaneously in all; nor are we at all sure of how much of the lesion represents compensation or actual functional disability. There is no doubt that a classification founded upon pathogenesis would clear matters considerably. (*e*) Many classifications are founded on lesions which afford too wide a field for interpretation. The predominance of a single feature, whether it be hyaline degeneration, granular degeneration, sclerosis or whatnot, determines to many eyes the biological "type." On the other hand, to others, the situation of the predominant lesion, whether in the glomeruli, the tubules, interstitium or vascular supply, or whether it is diffuse or focal, large or small, smooth or granular is the prime consideration. It is only exceptionally that we see a lesion limited entirely to one of the components of the kidney structure. The combinations are endless. Here again, it is the pathogenesis and not the end result which is the important consideration. The same criticism applies to the interpretation as to whether the lesion is focal or general.

Therefore, in order to understand and classify the nephropathies, it is essential to make observations, not over a short segment of the natural history of the disease, but over a far more extended period, preferably from the very beginning, and to correlate the clinical, functional, and pathologic findings in all phases of the disease. A clinician alone cannot do it; a pathologist alone cannot do it. It requires the closest coördination of the two. It matters little what names we apply, as long as we know what they represent. It is the genesis and not the picture at the autopsy table that will furnish the key to our understanding.

As far as our present knowledge of nephropathies permits us, therefore, a classification useful for the clinician, cannot, as I shall attempt to show, be based purely on clinical data or pathology or pathogenesis. In order to cover all or at least most of the nephropathies, a classification embracing combinations of these standards seems necessary. As far as real inflammations of the kidney are concerned, pathogenetic standards are all-sufficient, and on this basis we may say at once that the nephritides fall into two large groups: (1) The glomerulonephritides; (2) arteriocapillary fibrosis. Each of these groups has clinical subdivisions, the nature of which will be discussed subsequently.

These two groups cover more than nine-tenths of all nephropathies belonging to internal medicine. The remainder are comprised under the newly introduced term "nephrosis," a term unfortunate in its conception, but useful, as I shall attempt to show,

as a purely clinical designation. Its pathology will be elucidated in the course of the paper. These three main divisions will now be discussed.

Nephrosis. In most current textbooks the following lesions are grouped under this heading: (1) Fatty degeneration; (2) lipoid degeneration; (3) amyloid degeneration; (4) hyalin degeneration; (5) albuminous or granular degeneration; (6) necrotic kidney (bichlorid poisoning); (7) kidney of pregnancy; (8) chronic parenchymatous nephritis.

I believe the term "nephrosis" has tended to confuse the issue rather than clarify it, and for the following reasons. (*a*) Many have gained the impression that "nephrosis" is a new disease and not merely a name to cover a number of old things. (*b*) The term has come to convey different meanings. To some a "nephrosis" conveys its original sense, that is, noninflammatory or "degenerative" lesion and limited entirely or almost entirely to the tubular component of the organ. To others, it represents any disease of the kidney in which an anatomic *restitutio ad integram* is possible; and finally, to others, a "nephrosis" is a clinical entity and represents any disease of the kidney in which a certain group of symptoms, especially edema, is present.

It is not my purpose to plunge into a discussion of such a tender subject as "inflammation," except to point out that our continental confrères have a mechanistic concept of inflammation while ours is more biological. Although they recognize that an inflammation represents a tissue reaction against injury, Ribbert, Herxheimer and Fahr, for instance, cannot conceive of any reaction to injury without an accompanying cellular reaction on the part of the bloodvessels; in other words, they introduce the concept of repair. We, on the other hand, are inclined to the view that the mere defensive reaction of the tissue to injury solely represents inflammation, and that repair while a usual accompaniment, is not necessarily a part of the process. In other words, a socalled "degeneration," that is, a parenchymatous inflammation in the sense of Virchow, may in itself represent an inflammation. Indeed, Aschoff believes that even an epithelial cell can be inflamed, that is, partake of characteristics that represent a defensive reaction. Surely degeneration and inflammation are closely related, and it is difficult to say where one stops and the other begins.

However, no matter what concept one is willing to accept as to the dividing line between degenerations and inflammations, and no matter what definition of "nephrosis" one upholds, the grouping of these eight varieties under the general heading "nephrosis" is not consistent.

Etiologically they vary widely, and clinically, they have little in common. Even edema is inconstant. One cannot even say that a complete *restitutio ad integram* is possible in all. Here again

we must make a sharp differentiation between healing in the clinical sense and healing in terms of morbid anatomy. A lesion may heal in the sense that it is no longer progressive and gives no subjective or objective evidence of disease, yet some form of damage remains. While we can conceive that some lesions such as fatty and granular degeneration, may be followed by complete functional and anatomic restoration, we do not believe that a restoration to the histologic normal can take place in hyaline and amyloid degeneration and the necrotic kidney of bichlorid poisoning. In fact, we are so surprisingly uninformed as to the ultimate fate of such kidneys in which clinical healing has occurred, that one needs tread softly upon this debatable ground. Furthermore, even if a "nephrosis" is a lesion limited to the tubular or parenchymatous component of the kidney, the proponents of the term "nephrosis" perform a neat straddle, for in the chronic forms many (Fahr,[1] Volhard,[2] Munk,[3] Kaufmann[4]), describe profound productive changes in the glomeruli as usual accompaniments. Indeed, their descriptions resemble so closely those of glomerulonephritis, that one wonders whether they have not put the cart before the horse, especially in view of the fact that, as far as I can judge, their descriptions of the associated parenchymatous changes in what they regard as true glomerulonephritis is almost identical. Munk and Volhard admit that anatomically "nephrosis" and chronic glomerular nephritis are identical. Even clinically they are alike except in the matter of blood pressure. In nephrosis it is low and in glomerulonephritis it is high. Volhard stretches his theories somewhat unduly in order to explain this difference in blood pressure. As an advocate of the primary glomerular origin of hypertension, he conceives that in nephrosis, the disease begins as a degeneration and that the glomerulonephritis is secondary, while in glomerulonephritis, the glomerular lesion is primary, and the "nephrosis" is secondary to a hypothetical spasm of the glomerular capillaries and arterioles. In short the same anatomic lesion is caused by two diametrically opposite methods. It is difficult to follow this reasoning, for we all know that in the latent stage of proven glomerulonephritis, hypertension may be absent. Supposing even that hypertension is due to disease of the glomeruli and arterioles, why is hypertension present if the disease in the glomeruli is primary, and absent if it is secondary? Löhlein[5] and Herxheimer[6] regard some of the nephroses described by Volhard and Fahr as instances of true glomerulonephritis and I believe they are right.

Also, in the kidney of bichlorid poisoning all admit that inflammatory lesions represented by exudations occur, and are a prominent feature in the morphology. It is not necessary to cite further examples. A differentiation between nephroses and inflammations based upon tubular or extratubular involvement of kidney structure lacks consistency.

The problem of "nephrosis" as a generic entity is continually clouded by the fact that the varieties of this nephropathy are only rarely found in the pure state. Granular degeneration of greater or lesser degree is found in association with nearly all nephropathies. Amyloid, lipoid, and hyalin degeneration are commonly found together. Few kidneys show pure hyalin degeneration. Some degree of fatty degeneration of the kidney in association with other lesions is so common as not to be regarded as especially abnormal. Furthermore, the various lesions included among the nephroses may be accompanied by changes in the glomeruli or even the grosser vascular supply of the organ. In order to classify these mixed forms, one must evidently take into consideration many factors: the predominance of the lesion, one's interpretation of the pathogenesis, the clinical and functional data, and, if possible, the etiology.

We come now to an important and not uncommon variety of nephropathy, to which the name "nephrosis" is being more and more applied. I refer to the disease to which Epstein[7] has called particular attention in numerous papers published since 1917. Clinically, the disease progresses slowly; the urine is diminished, of high specific gravity and contains enormous quantities of albumin. Edema is marked. Epstein found interesting blood changes. There is an inversion of the albumin-globulin ratio in the serum. There is a constant increase in the blood cholesterol; in some cases it is so high that the blood serum is milky. The blood pressure is low, and the basal metabolism is usually shifted to the minus side. We see a number of such cases in the course of a year in Mt. Sinai Hospital and have come to recognize the symptom complex readily. What is the pathology of this complex? Epstein originally assumed that it was a "nephrosis" in the original conception of this term, that is, a parenchymatous or tubular degeneration of the kidney. However, he does not regard the malady as entirely renal in origin, but a disorder of metabolism, and that it is somewhat allied to myxedema.

In the past years cases of Epstein's nephrosis have come to autopsy in Mt. Sinai Hospital. We find that this symptom complex has been associated with different autopsy findings. We found the following renal lesions: (1) Pure or almost pure parenchymatous inflammations or granular degeneration;* (2) typical subacute or chronic glomerulonephritis; (3) pure or almost pure lipoid kidney; (4) amyloid kidney. It is apparent therefore, that Epstein's nephrosis is not a disease, in the sense of possessing a definite anatomic substratum, but a symptom complex. The high-protein,

* Through the kindness of Dr. Herbert Wiener, I recently was privileged to study sections of a kidney from a patient who revealed the typical evidences of "nephrosis." With the exception of some hyaline change in the glomeruli, the kidneys showed a pure parenchymatous nephritis (large white or yellow kidney). The lesion was the most unalloyed of this character that I have ever seen.

low-fat diet which Epstein proposed on the basis of his chemical studies is certainly efficient in some cases and certainly fails in others. This suggests that the malady has different origins, and I venture to suggest that it may eventually serve to diagnose the pathogenesis of the nephrosis.

I shall not enter into the controversy as to whether any of these "nephroses" may result in contracted kidney, because, being obviously difficult to prove, there is little evidence at hand. Volhard and Fahr[8] believe they saw two cases of "lipoid nephrosis" which showed beginning contraction. Munk and Bohnencamp[9] each report a similar case. Löhlein and Herxheimer on the other hand regard Volhard and Fahr's cases as a typical glomerulonephritis, which in our experience seems likely. In any event, even if contraction can follow "nephrosis" how can Volhard and Fahr say that these "nephroses" do not represent an inflammatory reaction?

The entire conception of "nephrosis" seems to rest on an extremely unstable footing, and as Orth[10] pointed out many years ago, the introduction of the term was unfortunate for every one has his own conception of its meaning. The term, however, has become more or less rooted in usage, and it probably is not wise to abandon it entirely. If it is employed in an anatomic sense, one has the right to demand what specific form of "nephrosis" we are concerned with; whether it is a fatty degeneration, amyloid, hyalin, lipoid or glomerulonephritis. It would be wiser to retain the term to denote the clinical complex set forth by Epstein. The diagnosis of the morbid lesion underlying this complex must wait future studies.

The Glomerulonephritides. We are far clearer concerning the nature of the glomerulonephritides. The etiology is better known. The pathology has a sounder footing; the stages are clearer and the diagnosis is more certain. Yet there are wide gaps in our knowledge, affording opportunities for controversy. Some of these I shall try to discuss so as to indicate the direction along which further studies need be guided.

We will begin with the *acute form of diffuse glomerulonephritis.* The clinical features of this nephropathy are well known. Usually after a latent period following an infection the patient develops a low fever, oliguria, albuminuria with abundantly formed elements in the urine, especially blood; general edema, a moderate hypertension, and if the disease is severe, signs of uremia. The fate of such patients, an important circumstance, we shall reserve for the discussion on the pathogenesis.

Etiology. The streptococcus plays the most important role in the etiology of acute glomerulonephritis. By far the majority of the cases (125 out of 179) (Volhard) follow a peculiar low-grade infection of the tonsil. The tonsil is large, tender and red. The redness is not as fiery as that seen in the follicular forms, and spots are nearly always absent. The next most common streptococcus

infection causing glomerulonephritis is scarlet fever. It must not be understood that every renal affection following scarlatinal nephritis is a glomerulonephritis. The mild albuminurias probably represent the parenchymatous change—albuminous fatty, or both—so often noted in many other febrile affections. Even in the severe and fatal scarlatinal nephropathies, according to Wagner[11], Munk[12] and Schridde,[13] the lesion in the vast majority is a round- or plasma-celled infiltration, mostly periglomerular or perivascular, which Munk and others regard as the local expression of a general monocytic infiltration. Other causes have been ascribed as the causes of acute glomerulonephritis (skin infections, war, and so forth) but the tonsils and scarlatina account for practically nine-tenths of all cases.

There is still doubt as to the manner in which streptococcus produces the lesion. In the first place, it is well known that the nephritis does not usually appear when the streptococcus infection is most acute, but in the subsiding stage. Does this mean that the lesion was present from the very beginning and that it appeared clinically only when a certain stage of injury or reaction was attained or does the streptococcus elaborate a toxin which attacks the kidney in a manner which we do not yet understand? It seems to me significant that the streptococcus has, as far as I am aware, never been found in the lesions of acute glomerulonephritis, and is only demonstrable in the subacute form described by Löhlein[14] and Baehr[15] which is associated with an anhemolytic streptococcus endocarditis. This indicates that the nephritis in sore throat and scarlatina is not the result of a direct action of the streptococcus but due to the intervention of an intermediary product. It seems extraordinary, in this connection, that although we can reproduce experimentally almost every lesion produced by the streptococcus, only rarely has any one been able to produce a typical acute glomerulonephritis of the human type in animals. This may be due merely to a species susceptibility to scarlatinal toxin. Furthermore, there is another peculiarity about the sequential relation of acute glomerulonephritis to the streptococcus; and that is, the frequent progression of the lesion even after recovery from the scarlatina or the removal of all known foci. This is an unusual circumstance, for it is one of the accepted principles in pathology that an inflammation heals and becomes an end product when the focus has been removed.*

Does this imply that we have deceived ourselves in thinking we have removed all infective foci? Does it mean, as Lubarsch[16] claims, that the products of the inflammation in themselves form a secondary focus, forming a vicious circle; or do these streptococci possess

* The kidney is not peculiar in this respect. Witness the latency period of acute yellow atrophy of the liver following trinitrotoluol poisoning, so commonly reported in England and the development of the choroid granulomata of sympathetic ophthalmia, months and even years after injury of the ciliary body.

qualities and a mode of action that has thus far eluded us: certainly, from the point of view of etiology the precise relation of the streptococcus to acute glomerulonephritis requires future study.

Pathology. The essential feature of acute glomerulonephritis is a swelling of the glomerular tufts with eventual production of new connective tissue, which begins within the capsule of the glomerulus and spreads diffusely between the tubules to the surrounding parenchyma. Vascular lesions are prominent, especially in the middle and later stages of the disease, and reveal all the changes of an arteritis with intimal hyperplasia, hypertrophy of the muscular coat and productive infiltrations. This is the socalled "large white kidney" and for all practical purposes it is a granuloma. Unless healing takes place, acute glomerulonephritis is a progressive disease, and reveals stages, as determined by the senescence of the formed elements and the more widespread distribution of new connective tissue at the expense of the parenchyma. The final stage is a small red granular organ, the socalled secondary contracted kidney, which is exceedingly hard to distinguish even clinically from what we shall later know as primary or "genuine" contracted kidney. The "secondary" contracted kidney may sometimes be distinguished from the "primary" contracted kidney by the fact that senescence of the formed elements (because the patients does not live long enough) rarely reaches the maximum attained in the "primary" variety. In short, the kidney retains its resemblance to granulation tissue and not to scar.

The question arises, why do some acute glomerulonephritides pass into the subacute and chronic stages, while the majority, heal? A difference in severity does not explain this entirely; first, because clinically mild cases often heal; second, because even when the insult has ceased or the known focus or foci have been removed, there is often progression. Volhard believes that progression or subsidence depends upon whether or not the patient comes under treatment in the early stage when the symptoms are mild, for in his experience few cases treated in the early stage pass into the chronic form. As far as our experience goes, early treatment has little effect.

There arises a highly important problem. Is it possible for an acute glomerulonephritis to heal clinically, leaving no trace symptomatically or functionally, remain dormant for a period of five to thirty years, and then light up and cause death with all the phenomena of a "secondary" contracted kidney? This question is answered affirmatively by most clinicians, apparently without sufficient reflection. They reason as follows; an infection (nearly always an attack of scarlet fever) causes an acute glomerulonephritis; scarlet fever in early life is extraordinarily common; therefore, the nephritis of later years is the result of the scarlet fever. Let us examine this syllogism closely. We are asked to assume a number

of things: (1) That each attack of scarlet fever was accompanied by a nephritis, a manifest absurdity, because very few patients give a history of having had nephritis. (2) That even when there is no such history, the nephritis was overlooked. This is highly improbable because a scarlatinal nephritis even of slight grade gives sufficient gross evidence to be recognized. Moreover, we will admit that some, but not all may have been overlooked. (3) That every scarlatinal nephritis is a glomerulonephritis. Available testimony shows that this is the exception rather than the rule. (4) That the resulting scarred kidney lies dormant for many years, and then reverts to the morphologically active granulation stage of the secondary contracted kidney; for the secondary contracted kidney, as I have already pointed out, is not a scarred kidney but shows abundant evidences of progression. Now such a sequence of events, as far as I am aware, has no parallel in pathology. One can readily understand the direct progression of an acute glomerulonephritis into the subacute or even subchronic forms over a period of a few years, but it is hard to conceive of a progressive lesion healing and suddenly relighting after many years, unless a new insult has arisen. As far as my experience goes, there is always a clinical continuity between the acute and the terminal stage. There is never a complete cessation of signs and symptoms. At all events, even assuming that a contracted kidney may arise in later life from juvenile attacks of scarlet fever or other infections, it must be far less common than at present believed. In short, an acute glomerulonephritis either heals and stays healed, or it progresses and kills within a short time. Statistics in regard to the ultimate fate of scarlatinal nephritis bear out our contention. Duyvis,[17] in 1920, studied 30 patients from the epidemic in Amsterdam in 1906. Not one had actual nephritis. Hansborg,[18] in 1925, examined 284 patients with scarlatinal nephritis one to ten years after discharge, and found only one to be suffering from a chronic nephritis, the characters of which distinguished it from that of scarlatina.

Curiously enough, common as scarlatinal glomerulonephritis is, we do not know the healed stage pathologically. Since a healed acute glomerulonephritis is a productive inflammation it must leave scars. In our experience, such kidneys are hard to obtain. We must be sure of a number of things: (1) That the patient had a true glomerulonephritis; (2) that there was clinical healing; (3) that no other form of renal nephropathy intervened. The problem will probably be solved in the next generation, since it is only in recent years that the recognition of acute glomerulonephritis has become fairly accurate.

Pathogenesis. In recent years there is a trend away from the conception of glomerulonephritis as a primary nephropathy and many (Kylin,[19] Munk, Umber,[20] Nonnenbruch,[21] Hirsch,[22] Siebeck[23] contend that it represents merely the local expression of a general

vascular and, more particularly, capillary disease. There is no question but that glomerulonephritis begins and proceeds as a vascular lesion. This is evidenced by the bloodless and swollen glomerular capillaries, the swelling and growth of the intracapillary and pericapillary endothelium, the intracapsular and extracapsular exudations and infiltrations, the marked evidences of arteritis. These lesions form practically the entire picture throughout all stages. What are the evidences showing that there is a generalized capillary disease? (1) It is difficult to explain certain clinical signs and symptoms, for instance, the hypertension and early edema, if the lesions were limited to the kidney alone.* (2) That general edema is usually present before any gross signs of nephritis become manifest, suggesting impaired capillary permeability. (3) That arterial hypertension frequently occurs before signs of nephritis appear. Kylin's observations in this regard are important. He found in a number of cases of scarlet fever that there was marked increase of capillary pressure for days preceding the evidences of nephritis. (4) Weiss[24] showed by capillaroscopy that the capillaries in acute glomerulonephritis, even in the early stages are swollen, tortuous, dilated and that the bloodflow is slower and granular.

No one, as far as I know, has made a consistent study of the pathologic morphology of the peripheral capillaries in glomerulonephritis, but there is every prospect that such studies would be futile. The structure is so delicate that any change especially with present methods of preparation, could not be detected. Only when massed together and well differentiated, as in the glomeruli or the islands of Langerhans, are capillary lesions readily seen.

These evidences at least suggest, but by no means prove that glomerulonephritis represents a general capillary disease, of which the kidney lesion is the local expression. Whether the extrarenal capillary involvement is simultaneous with the renal or as Volhard claims, consequent to the renal involvement, is a matter of opinion. At all events, additional support is furnished for the theory of the vascular origin of glomerulonephritis by the study of the vascular lesions of glomerulonephritis. Even in the early stages of acute glomerulonephritis lesions in the smaller arteries are manifest. We find swelling and hyperplasia of the intima with hypertrophy and infiltration of the muscular coat. In the advanced stages, as organization proceeds the vessels attain the typical picture of arteriosclerosis. A number of questions arise: Are these vascular lesions primary as Volhard believes, and do they represent a reaction to the insult which caused the nephritis? Are they secondary to the local

* If the nephritis were primary and the hypertension secondary, why does the hypertension disappear after the acute stage of the disease is over, even though the albuminuria and other functional renal signs persist, only to reappear in the stage of the "secondary" contracted kidney?

inflammation or to a systemic factor produced by the nephritis? Much dialectic has been expended in discussing the pros and cons of these questions, and a satisfying answer is not yet at hand. One can understand that the lesions in the intima may be the result of a local or general toxin, for we know that marked thickening and hyperplasia of the intima is found almost invariably in the vessels neighboring upon an inflammatory focus, (for instance, an abscess) but the marked muscular hypertrophy cannot be explained on any such basis. I venture the following explanation: that the hypertrophy of the muscularis is compensatory to the hypertension, just as left ventricular hypertrophy. My reason for this belief is based upon a not uncommon observation to which I have called attention in a previous paper and to which the name "transient arteriosclerosis" may be applied. A patient with acute glomerulonephritis develops hypertension. The radial vessels feel thickened to such a degree, that even skilled clinicians have diagnosed a previous arteriosclerosis. This sensation of thickening is not the result of the increased tension, for it persists for some weeks after the tension has reached normal. I believe there was actual thickening; that this thickening was due to hypertrophy of the muscularis, and that the hypertrophy disappeared when the inciting cause, the hypertension, disappeared. This observation is in accord with the work of Schlayer[25] who states that it is not the intimal changes that make an artery palpable, but the functional changes in the media which may not even be visible anatomically. It is comparable to the muscular hypertrophy seen in any hollow viscus behind a stricture. It may be well to call attention at this time to the fact that thickened vessels may persist even when the glomerulonephritis has healed and the hypertension has disappeared. I have seen a number of examples of this sequence in people so young that an arteriosclerosis could not be expected. In these, we must assume that organization of the vessels had taken place. It will be profitable to learn the fate of these patients.

There is little need to enter into the discussion of the particular form of glomerulonephritis associated with subacute bacterial endocarditis. It has been so fully set forth in the writings of Löhlein, Baehr and Libman that its clinical bearings, pathology and pathogenesis form one of the most settled chapters among nephropathies. It will suffice to say that it is essentially an embolic process and that pathologically it can be sharply differentiated from the other glomerulonephritides.

Arteriocapillary Fibrosis. This, by far the most common form of nephritis, has received so many names that even its best friends have difficulty in recognizing it. We shall mention only those most in use. Sclerotic kidney; primary contracted kidney; genuine contracted kidney; chronic, diffuse nephritis; hyperplastic nephritis, granular kidney (small and large red), innocent contracted kidney;

malignant contracted kidney; hypertensive kidney; arteriosclerotic kidney. As one may note, the standards of classification are various, being now clinical, now physical, now pathological or combinations of these. It is not to be understood that all observers regard these varieties as identical; indeed with the present misdirected zeal to create new "types" they introduce not only subgroups, but even attempt to differentiate them from one another. One of my main objects is to try to show that on a strict morphologic and pathogenetic basis, they all represent one and the same thing.

It seems to me that the greatest error that these observers have made has been to regard the product they find at autopsy as the end result and not merely a stage of a progressive process in which the beginning and the end are discernible. One can readily place in series kidneys in which each stage merges imperceptibly with the preceding. Thus the earliest stage is represented by a kidney which grossly is normal, but in which the glomeruli show a little hyalin or productive change. The arterioles, especially the vasa efferentia, show a little thickening. In the next stage, these lesions are more widespread; young periglomerular connective-tissue foci appear in the form of round-celled proliferations; the vessels begin to show more advanced stages of arteriosclerosis. The kidney is perhaps a little firmer, but grossly it still appears practically normal. Next, the connective tissue is older and spreads from around the glomeruli between the cortical tubules. Sclerosis of the arterioles is more marked and the larger renal vessels become involved. The kidney now becomes what is known as the large "granular" kidney. In the succeeding stages, the senescence and more widespread distribution of these elements, causes a slow progressive shrinking of the organ; the tubules become deformed and disappear as the result of the fibrous-tissue replacement. In these stages, the granules become coarser, and the term "small granular" kidney becomes applicable. Finally the connective tissue becomes more and more fibrous until the kidney is a veritable scar; the vessels show the classical lesions of a profound arteriosclerosis; the tubules dwindle in number until only a portion of their original number remain, and we obtain the only real end stage, the atrophic contracted kidney.

The reason why the intermediary stages were regarded as end products is because observers failed to realize that the patient with nephritis dies, in 9 instances out of 10, not as the direct result of the nephropathy (uremia) but rather from extrarenal causes, primarily vascular and cardiac accidents which are secondary to influences independent of the nephritis. In other words, the stage of the lesion found at autopsy depends almost entirely upon the time when the cardiac vascular break occurs. The tempo of the disease varies widely, a subject that we shall discuss later. This conception

subsumes the proposition that the kind of nephritis we are describing is not primary, as had hitherto been regarded, but secondary. As the discussion of this postulate involves the most important symptom of this variety of nephritis, namely, hypertension, a short summary of current views upon this symptom is necessary. Until recently, the usual association of hypertension on the one hand and nephritis and arteriosclerosis on the other led to the still conventional belief that hypertension was caused by these lesions. It did not explain a number of things: (1) Why the degree of hypertension bears no relation whatever to the degree of the renal or vascular lesion. (2) Why hypertension, even sufficient to cause death, is sometimes present, with renal and vascular lesions that are insignificant. This combination has been called by some "essential" hypertension.* (3) Why lesions of severe grade in the kidney and vessels are sometimes found at autopsy, although hypertension was not present. This combination is not uncommon after the age of fifty-five, and is called by Allbutt "decrescent" nephritis and arteriosclerosis, and by others "arteriosclerotic" kidney.

What then is *the relation of hypertension to nephritis and arteriosclerosis?* An observation made many years ago led to a significant train of thought. In the course of a routine examination a hypertension is found without any attendant signs of nephritis or arteriosclerosis. Soon albumin appeared in the urine. In the course of the next years all the classical signs and symptoms of nephritis and arteriosclerosis develop, cardiac signs appear, coronary disease develops, and the patient years after the onset dies of cardiac failure. This observation I have made a number of times and I am sure has been frequently seen by others. This led to the thought that perhaps the hypertension is first and the nephritis and arteriosclerosis follow. In other words, instead of abnormal function following morbid anatomy structural change follows abnormal function. This concept finds corroboration in another series of observations.

In previous papers,[26,27,28,29] I have discussed the causal relation of arteriosclerosis to hypertension, and cited twelve proofs to show this relation. I merely wish to recall two of the more important arguments. (1) That neuroretinitis is never present unless there is or has been hypertension. No form of nephritis unaccompanied by hypertension is associated with a neuroretinitis. Inasmuch as a neuroretinitis is a lesion representing arteriosclerosis and its sequelæ, it is reasonable to conclude, that it is not the nephritis but the hypertension that is the cause. (2) A more cogent argument is the pathogenesis of arteriosclerosis of the pulmonary circulation.

* It may be well to define "essential" hypertension. By some it refers to a hypertension without or with little evidence of clinical nephritis. By others it refers, as I do, to hypertension without anatomic nephritis. As clinical and anatomic nephritis as I shall show are two different things, it would be well for writers to define their meaning when they employ this term.

Arteriosclerosis of the lesser circulation is practically never found unless such disease is present as will cause increased tension within the pulmonary vessels. Such an increased tension is most common with mitral stenosis, less frequently with bronchitis, emphysema, asthma and kyphoscoliosis. In such cases the arteriosclerosis of the pulmonary vessels is extreme no matter how young the patient, while the arteries of the greater circulation show no arteriosclerosis. On the other hand, if there is hypertension in the peripheral circulation, the aorta and its branches show arteriosclerosis, while those of the pulmonary circulation show none. The observation is doubly important not only because it shows that increased tension causes arteriosclerosis but also because, it makes one skeptical of the constantly recurring statement that infections cause arteriosclerosis. It seems to me that any discussion of the etiology of arteriosclerosis misses fire that does not take into consideration this difference in incidence between arteriosclerosis in the greater and lesser circulations. The etiology of pulmonary arteriosclerosis has additional significance in regard to the relation of arteriosclerosis to nephritis. This will be discussed later.

There probably are other causes of arteriosclerosis, but I think there can hardly be any question but that intravascular tension is one of them. This is admitted by many observers (Allbutt,[29] Monakow,[30] Munk, Pal,[31] John,[32] Kylin,[33] Faber[34]).

The Relation of Arteriosclerosis to Nephritis. Since the studies of Gull and Sutton, pathologists are now fairly well agreed, that arteriocapillary fibrosis represents a disease of the vascular framework and that the parenchymal changes are largely the result of the consequent impoverishment of the blood supply. (Jores,[35] Löhlein, Volhard, Fahr, Munk, and others.) Furthermore, as Jores has shown, the vessels in other organs beside the kidney show profound arteriosclerosis, notably in the brain, the heart, the spleen, the skin, the retina and the pancreas. In consequence, we must view this form of chronic nephritis not merely as a local vascular disease but as an expression, probably the most prominent, of a general vascular disease. Indeed, clinically, the extrarenal lesions are of far greater consequence than the renal, for it is these lesions that cause the bulk of signs and symptoms, and in nine-tenths of the cases—death. It is curious that the brunt of the lesion should fall more upon one organ than upon the other, and why one patient will die of apoplexy, another of coronary disease or heart failure and another of uremia. Finally, not only must we view this form of chronic nephritis as a malady of the larger vessels, but of the capillaries as well. Certainly the glomerular changes have every appearance of what I have termed "arteriosclerosis in miniature." The endothelial thickenings and proliferations, the fibrosis and hyalin degeneration of the walls of the capillaries, the eventual calcification—all strongly suggest this description. The strongest link in the chain of evidence is the

work of Weiss, showing that the peripheral capillaries as viewed by capillaroscopy are diseased.* So in this malady also, as in glomerulonephritis, we infer that there is a general capillary arteriosclerosis. In all probability this accounts for some of the cases of diabetes associated with hypertension disease, since there is nearly always disease of the capillaries of the islands of Langerhans.

For these reasons, I believe the term arteriocapillary fibrosis first employed by Gull and Sutton, is better than those conventionally used. With the identity of chronic nephritis and arteriosclerosis reasonably well established, these lesions do not bear mutual reactions upon each other, as some declare, but are simultaneous reactions to the same insult.

What is the cause of the hypertension? We do not know. Elsewhere I have described a type of patient, in whom hypertension is apt to occur, largely the result of psychic characteristics. It is also not an uncommon sequence to Grave's disease, a malady that is also largely the result of psychic influences. If the usual hypertension of Grave's disease persists, clinical and pathologic evidences of arteriocapillary fibrosis eventually arise. Recently, I described cases of primary hypertension and secondary nephritis and arteriosclerosis in juveniles who had a congenital peripheral resistance in the form of either congenital stenosis of the aorta or congenital narrowing of the bloodvessels.

How are we then to account for the "decrescent" kidneys, kidneys that show more or less marked sclerosis at autopsy although hypertension was slight or absent? These kidneys have also been called "benign" sclerosis as opposed to the "malignant." Here a qualification is necessary in regard to the etiologic significance of hypertension; for if hypertension, which is an exaggeration of normal tension, may cause arteriocapillary fibrosis, there is no reason why a long continuing normal intravascular pressure may not do the same. That is why such kidneys occur in the aged. We find the analogue of this in the pulmonary circulation, for Ljungdahl[36] and I have found that arteriosclerosis of the pulmonary vessels does occur in the senile, even when mitral stenosis and so forth, is absent. It is largely a question of tempo. Hypertension causes arteriosclerosis and nephritis sooner than does tension. The question of tempo in hypertension and its consequences is a baffling one. Why do some patients go to pieces within a year or two after their hypertension is discovered while others live ten, fifteen or more years? The answer to the question probably involves fine compensatory adjustments. The one form has been called "malignant" and the

* One of the most exquisite examples of capillary sclerosis consequent to increased tension is seen in long-standing cases of mitral disease. Here not only do we find arteriosclerosis of the larger pulmonary vessels, but the capillaries of the alveolar walls show marked thickening and hyaline change with considerable increase of the interstitial connective tissue. This is the lesion called "Stauungsinduration" and it represents an arteriocapillary fibrosis of the lung.

other "innocent" and this term has been transferred, especially by those who believe the renal lesion is the beginning of all things, to the kidney found at autopsy. This distinction is not strictly valid, for in my experience all permanent hypertensions are malignant; it depends upon whether the patient lives long enough for the hypertension to cause sufficient functional damage to be responsible for death. In fact, the proponents of the theory that the kidney is the primary source of the hypertension admit the transition of the innocent hypertension into the malignant forms. Volhard and Fahr explain this as due to changes that occur in the kidney. As the result of an hypothetical ischemia which suddenly enters into the pathogenesis, inflammatory changes modify the picture, so that, in their estimation, the "malignant" granular contracted kidney is a "combination" form of sclerosis plus nephritis. They add the synonym "genuine" contracted kidney to this form. Frankly, their description of the superimposed inflammatory lesions, the result of this supposed ischemia, is by no means convincing. Practically all of these newer lesions represent, as far as I can note, merely exaggerations of the already present morphologic elements of the sclerosis. Indeed, MacCallum,[37] Löhlein[38] and Rosenthal[39] among others regard the socalled arteriosclerotic kidney unassociated with hypertension (innocent type) as morphologically identical with the genuine form (malignant type) associated with hypertension. In short, they are all arteriocapillary fibrosis.

From these premises, one gathers that clinical nephritis and anatomic nephritis are separate things, and that functional tests afford no guide to the diagnosis of the extent and degree of damage in the kidney. In previous papers, I have called attention to the fact that the functional tests are far more dependent upon extrarenal rather than the renal factor and especially upon whether the patient's circulation is in a condition of compensation or decompensation. A functional test indicates the renal function at the time the test was taken, and is almost entirely a prognostic guide.

On the basis of our observations we submit therefore the following classification of the strictly medical nephropathies:

1. Nephrosis. (*a*) Chronic parenchymatous nephritis (degeneration?); (*b*) lipoid kidney; (*c*) amyloid kidney; (*d*) subacute glomerulonephritis; (*e*) unknown origin.

2. Glomerulonephritis. (*a*) Acute; (*b*) subacute; (*c*) chronic.

3. Arteriocapillary Fibrosis. (*a*) With hypertension; (*b*) without hypertension.

Conclusions. 1. A classification of the strictly medical nephropathies is submitted which is based partly upon pathogenesis and partly upon clinical facts.

2. The use of the term "nephrosis" has no consistent pathologic substratum and is therefore merely a clinical entity. When the term is used, it should always bear a qualification as to what variety of "nephrosis" is meant.

3. Nephritis is a disease with a life cycle. This applies to the acute as well as to the chronic forms. The phenomena during a certain period of observations are not to be judged as end results, but as representing a stage of a process, in which clinically the beginning and terminal phases may be quite different, these representing the socalled "types" of the disease. In order to evaluate conditions, it is essential to know what has gone on before. Therefore, the only satisfactory method in studying the problem of nephritis is the observing of cases from the beginning to the end. It is essentially not a hospital problem but one for the general practitioner.

4. Anatomic and clinical nephritis are two different things, and are not to be judged in the terms of the other. In most instances, especially in the arteriocapillary fibrosis, the diagnosis is therefore to be expressed in terms of function rather than in those of anatomy.

5. There is need of greater definition of terms currently employed in the discussion of nephropathies. This applies not only to the term "nephrosis" and "nephritis" but to the expression "essential hypertension" or "hyperpiesia."

6. Evidence is again brought forward to show the sequential relation of nephritis and arteriosclerosis to hypertension. Nephritis and arteriosclerosis are the same disease, and represent contemporaneous reactions to the same insult, namely, hypertension. The term "arteriocapillary fibrosis" is suggested to cover these pathologic reactions.

7. In this disease the primary pathologic change is almost entirely a vascular one. There is evidence to show that acute glomerular nephritis also represents a generalized capillary disease, in which the renal lesion is the localized expression, perhaps the most predominant one. There is evidence to indicate that the hypertension is the direct result of the increased resistance due to the capillary disease and that the sequential relation of hypertension to the nephritis is only specious.

BIBLIOGRAPHY.

1. Fahr: Path. Anat. des Morbus Brightii. Hand. der spez. Path. Anat. und Hist., Berlin, 1925.
2. Volhard: Die doppelseitigen hämotogenen Nierenerkrankungen, Berlin, 1918.
3. Munk: Pathologie u. Klinik der Nierenerkrankungen, Berlin, 1925.
4. Kaufmann: Lehbuch der pathologischen Anatomie, Berlin, 1911.
5. Löhlein: Deutsch. med. Wchnschr., 1918, **44**, 851, 1187.
6. Herxheimer: München. med. Wchnschr., 1918, **65**, 283.
7. Epstein: J. Am. Med. Assn., 1917, **69**, 444.
8. Volhard and Fahr: Die Brightsche Nierenkrankheit, Berlin, 1914.
9. Bohnencamp: Virchow's Arch. f. path. Anat., 1922, **236**, 380.
10. Orth: Quoted by Munk.
11. Wagner: Deutsch. Arch. f. klin. Med., 1880, **25**, 529.
12. Munk: Virchow's Arch. f. path. Anat., 1919–1920, **227**, 210.
13. Schridde: Beitr. z. path. Anat., 1912–1913, **55**, 345.
14. Löhlein: Med. Klinik., 1920, **10**, 375.
15. Baehr: Proc. New York Path. Soc., December, 1911, 11, 123.
16. Lubarsch: Pathologische Anatomie, edited by Aschoff, Jena, 1913.
17. Duyvis: Nederlandsch. Tijdschr. v. Geneesk., 1919, **11**, 1339.

18. Hansborg: Acta Med. Scandinavica, 1925, **61**, 481.
19. Kylin: Acta Med. Scandinavica, 1921, **55**, 368.
20. Umber: Deutsch. med. Wchnschr., 1923, **49**, 369.
21. Nonnenbruch: Ztschr. f. klin. Med., 1919, **87**, 397.
22. Hirsch: Deutsch. med. Wchnschr., 1916, **42**, 715.
23. Siebeck: Die Beurtheilung und Behandlung der Nierenkrankheiten, Tübingen, 1920.
24. Weiss: Deutsch. Arch. f. klin. Med., 1916, **119**, 1.
25. Schlayer: Deutsch. Arch. f. klin. Med., 1910, **98**, 164.
26. Moschcowitz: Am. J. Med. Sci., 1919, **158**, 668.
27. Moschcowitz: Arch. Int. Med., 1920, **26**, 259.
28. Moschcowitz: J. Am. Med. Assn., 1921, **77**, 1075.
29. Moschcowitz: J. Am. Med. Assn., 1922, **79**, 1196.
30. Monakow: Deutsch. Arch. f. klin. Med., 1920, **133**, 129.
31. Pal: Wien. klin. Wchnschr., 1921, **71**, 967.
32. John: Med. Klinik., 1913, **9**, 942.
33. Kylin: Klin. Wchnschr., 1923, 2, 2064.
34. Faber: Die Atherosklerose, Jena, 1912.
35. Jores: Deutsch. Arch. f. klin. Med., 1908, **94**, 1.
36. Ljungdahl: Arteriosklerose des kleinen Kreislaufs, Wiesbaden, 1915.
37. MacCallum: Text Book of Pathology, Philadelphia, 1917.
38. Löhlein: Beitr. z. path. Anat., 1916-1917, **62**, 570.
39. Rosenthal: Deutsch. Arch. f. klin. Med., 1920, **133**, 153.

EXPERIMENTAL NEPHRITIS PRODUCED BY IRRADIATION.

By F. W. Hartman, M.D., Adolph Bolliger, Ph.D.,
and
H. P. Doub, M.D.,
Detroit, Mich.

(From Departments of Pathology and Roentgenology, Henry Ford Hospital, Detroit.)

Although the experimental nephritides produced by various nephrotoxic substances, recently reviewed in a comprehensive way by MacNider,[1] have added much to our knowledge of the functional and anatomic changes, clinical nephritis is not reproduced. Further, the subacute and chronic changes have not been consistently produced by these substances.

The usefulness of an agent which will readily give a nephritis that may be controlled as to the acute, subacute or chronic stage is apparent.

The lesion should preferably be obtained in an animal large enough for complete functional studies and without disturbing the normal position of the kidneys.

Allen[2] has recently found partial nephrectomy coupled with functional overstrain gives satisfactory reproduction of chronic nephritis working with dogs, sheep and goats.

In 1904 Linser and Baermann[3] reported albuminuria after irradiation of kidneys without alteration of the epithelium. Buschke and Schmidt[4] in 1905 by exposing the kidneys of rabbits directly

through a surgical incision obtained necrosis of both cortex and medulla in two animals seven to eight weeks after radiation. Other animals showed albuminuria but no pathologic changes. They failed to obtain any changes when the radiation was done through the skin and body wall. As pointed out by Warthin[5] the damage observed in the 2 cases was possibly due to operative trauma.

During the same year (1905) Schulz and Hoffmann[6] took up a more comprehensive study of the action of the Roentgen ray upon renal tissue. Like Buschke and Schmidt[4] these workers surgically brought the kidneys of rabbits up over the skin surface, removed the fatty capsule, and, after covering the whole animal with lead, radiated the kidney through a cylinder of lead. The dosage was measured and the kidneys examined histologically from one hour to forty-eight days after exposure. Neither functional or vascular studies were carried out.

Summarizing their work as seen in ten detailed experiments the early changes were hemorrhage and transudation throughout the interstitial tissue with congestion of the glomeruli and in some instances complete tubular disintegration. Following the destruction of the tubular epithelium the interstitial tissue increases in proportion until at the end of forty-eight days the picture was that of an early chronic interstitial nephritis. Secondary epithelial degeneration was due to pressure. The glomerular atrophy was also attributed to compression. Marked eosinophilic infiltration was noted. The bloodvessels were only mentioned as showing muscular hypertrophy and swelling.

The effect of the Roentgen ray upon the kidneys was reported at about the same time by Linser and Helber,[7] Rosenstern,[8] Warthin[5] and Krause and Ziegler.[9] Warthin[5] gave conclusive evidence of renal damage produced by prolonged radiation in both the experimental animal and leukemia patients. The lesions in the latter consisted of degenerative changes in the renal epithelium and deposits of lime salts. With the possibility of renal damage demonstrated he suggested repeated urine examinations in leukemias receiving Roentgen ray and stated that in a nephritic a dangerous exacerbation might be excited by radiation therapy.

Hall and Whipple,[10] in their studies of "Roentgen ray intoxication" state, "Careful examination of the kidneys of our series of animals at autopsy and of the microscopic sections has convinced us that if there is renal injury it is of relatively slight grade and is not a constant finding." Thus the question of kidney destruction was largely forgotten, and indeed a number of observers during 1923, 1924 and 1925 have advocated deep Roentgen ray therapy as a successful treatment for oliguria and anuria, Stephan[11] explaining that nephritis is a functional disturbance of the epithelium which may be removed by the stimulating action of the Roentgen ray.

In 1924 Martin,[12] while attempting to injure the adrenal through

a surgical incision with the Roentgen ray, irradiated the upper pole of the kidney and the marked interstitial change was shown in a microphotograph.

Exact localization upon the kidney combined with histological studies through the acute stage, subacute and chronic stages was carried out only by Schulz and Hoffmann[6] in rabbits.

During the course of investigations into the nature of the immediate metabolic reaction to deep Roentgen ray therapy, during the spring and summer of 1924, one of the animals (B) was allowed to live for five months after receiving, over the left costovertebral angle, 200 kilovolts, 4 milliampères at 50 cm. skin distance for a period of two hours. A deep ulcer 15 cm. in diameter developed and caused the death of the animal by necrosing through the peritoneum with the development of peritonitis. The only striking autopsy finding in addition to the peritonitis was the difference in the size and consistency of the kidneys. The left, weighing 17 gm., was one-third the size of the right and was covered by a thick, opaque, fibrous capsule which was firmly adherent to the cortical surface when the capsule was stripped. The kidney tissue was firm with a roughly granular surface. On section this kidney cuts with resistance. The surface is homogeneous, firm and glistening. The cortex is 2 to 5 mm. in thickness as contrasted with the cortex of 5 to 8 mm. in the opposite kidney. The striations are indistinct but the glomeruli are made out. The bloodvessels gape open and are thick-walled. Microscopically the tubules are almost completely replaced by interstitial tissue and those remaining are distorted and compressed. Comparatively the glomeruli are well preserved. However, many of them are hyalinized, and Bowman's capsule is many times the usual thickness. All of the bloodvessels are thick-walled and many of them have undergone complete endarteritis. The right kidney was larger than normal for a dog of 22 kilograms but was otherwise unchanged either grossly or microscopically.

The finding in this animal demonstrated for the first time that a chronic interstitial nephritis could be produced by exposure of the kidney through the abdominal wall without extensive damage to other organs. It suggested further the possibility of readily producing in the dog chronic kidney lesions suitable for the study of the nephritis problem. (Figs. 12, 13 and 14.)

Experimental. I. METHOD. The animals were healthy young dogs ranging from 17 to 35 kg. They were kept under observation for a minimum of three days before observations were started. Catheterized urine specimens were examined to rule out the presence of albumin, casts, red blood cells and leukocytes. Phthalein excretion was tested after the intravenous administration of the dye, and animals showing an output of less than 60 per cent in two hours were not used. A preliminary nonprotein nitrogen and urea on the blood of the fasting animal was done and those showing

NPN of 40 mg. per 100 cc. or less and urea of 18 mg. per 100 cc. or less were accepted for the experiments.

The dogs were divided into two groups. In the first (Group A) both kidneys were irradiated. In the second (Group B) one kidney was excised for histologic study and the remaining one irradiated. Each of these groups were subdivided, A^1 and B^1 receiving the Roentgen-ray in massive doses and A^2 and B^2 receiving the Roentgen ray in multiple smaller doses at intervals. Both the massive and repeated doses produced satisfactory lesions.

The Roentgen ray was applied over an area varying from 10 to 15 cm. square with the the costovertebral angle as the approximate center. The time of application varied from fifteen to sixty minutes, but 200 kilovolts, 30 milliampères and filtration with 1 mm. copper and 1 mm. aluminum at 50 cm. skin distance was used in all experiments.

Up to the present time 26 dogs have been used in this series. Of these 8 died acutely within a five-day period after exposure. Eighteen have been followed from one to thirteen months. Fourteen have come to autopsy. Not a single animal has failed to show kidney damage both from functional and histologic examination.

II. General Effects. Eight of the animals died soon after treatment as an immediate result of the heavy dosage and the large area exposed. In one-half of the surviving animals there was diarrhea, often bloody, for several days but later at autopsy only a few depressed scars were found, usually in the duodenum or first portion of the jejunum. The liver and spleen showed at times changes which will be dealt with in a later communication. Studies of the adrenals will be presented elsewhere. In most instances the hair in the exposed skin came out but later grew in again. Only in the one animal was a sloughing ulcer produced. After the acute stage the dogs usually gained weight and remained fat and sleek until the terminal stage.

III. Effects upon the Kidney. These may be divided arbitrarily for convenience in study into three stages, namely, acute, subacute and chronic.

(*a*) The acute stage is that described in most of the researches mentioned and was studied in eight of our animals which died acutely. Seen at the third to fifth day the irradiated kidney was larger than usual. The capsule was thin but stripped readily, leaving a smooth dark red surface with here and there recent blood extravasation on the cortical surface. The superficial bloodvessels are dilated and engorged. On section the cut surface drips blood. The tissue is dark grayish-red in color, soft and granular. The whole surface is œdematous but the normal architecture is made out. The glomeruli are seen as deep red dots. The pelvis is of usual size and the epithelium is smooth. Microscopically the bloodvessels are dilated and engorged throughout and inter-

tubular hemorrhages are numerous. The epithelium lining the tubules is swollen, granular, desquamating and takes the stain poorly. In some places the epithelium has separated entirely from the basement membrane. The glomeruli fill the capsular space and the capillaries are engorged. In many there is extravasation of blood and infiltration by round and wandering cells. (Dog N 14). (Figs. 1, 2 and 3.)

(*b*) The subacute stage was seen at four autopsies in animals living from four to eight weeks after the initial irradiation. The deaths were not wholly due to kidney insufficiency but to various complications, one from distemper, one from intestinal obstruction and two from suppurative nephritis. The kidneys showing the suppurative process (see Fig. 7) were larger than normal. The others were somewhat smaller. The capsule is thicker than usual and gray. It strips readily except over the abscessed areas. These areas are slightly elevated and grayish-yellow in color. In uncomplicated nephritis the cortical surface is smooth but lighter color than normal. On section the cortex ranges from 6 to 8 mm. in thickness. The whole surface is grayish-red in color and granular. The normal dots and striæ are rather indistinct. The pyramids are pale. The mucosa lining the pelvis is smooth except in the suppurative cases. Microscopically this stage is characterized by distorted and widely dilated tubules. Often they are seen as open spaces with a lining of flattened atrophic epithelium. In other cases the lumen contains homogeneous pink staining material or a few faintly staining epithelial cells. The glomeruli are comparatively well preserved but the tufts are often smaller than usual and there is an increase of pink-staining hyaline stroma at the expense of the capillaries. In a few instances the capsular space contains homogeneous, pink-staining, hyalinized thrombi. In the kidneys complicated by the suppurative process the picture is obscured over large areas by the dense polymorphonuclear infiltration and hemorrhage. (Figs. 4, 5 and 6.)

(*c*) The chronic stage is seen in those animals surviving longer than three months and most of these died from kidney insufficiency. In a number of these animals, even dogs only seven months old, the renal artery was thickened and rigid though not calcified. On section the wall is grayish-yellow in color and two to three times the normal thickness.

The capsule is quite gray and opaque. It is tense and strips, carrying some of the cortex away. The cortical surface is smooth, dark red in color and has a peculiar glassy translucence. It is dotted by small, slightly depressed, gray areas. On section it cuts with resistance leaving a dense, firm, homogeneous, fibrous surface which is grayish-red in color. The cortex is thin, ranging from 3 to 6 mm. in thickness, and the glomeruli are very numerous. The pyramids are homogeneous and lighter gray in color. Microscopic-

ally the most striking finding is the increase in interstitial tissue. Large areas, both in the cortex and medulla, show no tubules at all. Where found they are distorted, either being dilated or compressed. The dilated ones often contain homogeneous pink staining material. The lining epithelium where present is composed of flattened, desquamating or vacuolated cells. The glomeruli appear more numerous than normal and relatively well preserved. Bowman's capsule is very thick and contains only an occasional nucleus. The glomerular tufts are in various stages of hyalinization and atrophy but in many the capillaries are remarkably well preserved. The bloodvessels are thick-walled and many have undergone complete endarteritis. The intima is much thicker than usual and appears corrugated. In two instances blue-staining deposits were found, once in the medulla and a second time scattered throughout the cortex within the capsular space.

IV. Functional Changes. The functional changes consisted of albumin and granular casts in the acute stages. Albuminuria persisted throughout the experiment but casts were often difficult to find after the acute stage. The excretion of phthalein was slowly depressed until in the final stages no dye was excreted at all. The water excretion was striking because of the marked polyuiria with low specific gravity in the subacute stages and the oligura or anuria with fixed low specific gravity in the final stages. Changes in the blood chemistry were typical, showing retention of nitrogen beginning only in the subacute stages and persisting throughout the experiment, usually mounting to great heights during the final stages. (Figs. 7, 8, 9, 10, 12, 13, 14, 15 and 16.)

V. Constitutional Changes. (*a*) Nutrition: As stated previously the nutrition of the animal usually improved throughout the experiment. They were given food consisting principally of meat (raw and cooked) with water *ad lib.* except during observation periods. Under this regime the animals usually gained weight and were in excellent nutrition until the final stages of the experiment when they were vomiting and unable to retain either food or water.

(*b*) Vascular changes: Were followed closely using the auscultation method of Allen[13] throughout the subacute and chronic stages and it was found that the blood pressure slowly increased, the diastolic increasing relatively more than the systolic, so that in the final stages systolic blood pressure reached 230 and the diastolic 150 in some instances.

(*c*) Eye changes: In those animals showing marked increase in blood pressure socalled albuminuric retinitis and fresh and old hemorrhages were observed.

(*d*) Edema: Pitting edema was not observed in any of the animals but at autopsy a peculiar, glassy, edematous panniculus was occasionally observed.

(*e*) Acidosis: The CO_2 combining power of the plasma fell as

low as 5 per cent in a number of the animals just before death and the inorganic blood phosphates of the plasma ranged from 10 to 19 mg. per 100 cc. blood.

(*f*) Blood: There was an early relative lymphocytosis and eosinophilia. Later anemia developed usually with a low-color index. In a single instance a macrocytic anemia with many regeneration forms and hyperplastic bone developed. This phase is now under further investigation.

VI. The principal complication encountered in the kidney was an acute suppurative pyelonephritis occurring usually in the subacute stage. Here the affected kidney was densely infiltrated by miliary abscesses and hemorrhage. The pelvis was dilated and along with the ureter was filled with thin purulent material. This complication occurred in five animals of the series and occurred more often in those which were catheterized frequently, but a few uncatheterized were similarly affected. The suppurative process was accompanied by leukocytosis and the animals died within a few days with rapidly depressed renal function. (Fig. 6.)

In two animals perforating gastric ulcers were found and an accompanying peritonitis.

PROTOCOL—N 14. Female shepherd mongrel weighing 17 kg.

March 24, 1925. Nonprotein nitrogen of the blood was 38 mg.; urea nitrogen, 14 mg. Received forty-five minute exposure of 200 kilovolts, 30 milliampères at 50 cm. skin distance over each flank in an area 15 cm. square with only 0.5 cm. copper filtration. Following the irradiation the appetite was poor and beginning the second day there was vomiting and diarrhea.

March 27. Nonprotein nitrogen of the blood was 24.9 mg. and urea nitrogen, 11 mg.

March 28. The animal is found dead.

Autopsy. On opening the abdomen and thorax the serous membranes are dry and lusterless. The lungs are air-containing but the heart is dilated. The intestines are lighter in color than normal and on section the mucosa of the small intestine is thick, pale and friable as though it had been cooked. Cracks and furrows are seen but no ulceration.

The kidneys are somewhat larger than normal. The capsules strip readily, leaving smooth, reddish-brown, cortical surfaces. On section the cortex is grayish-red and granular. The dots and striæ are indistinct. The mucosa lining the calices and pelvis is congested.

Microscopic. The bloodvessels are dilated and engorged. The glomerular tufts are swollen completely filling the capsular space and show intense congestion along with round and wandering-cell infiltration. The tubular epithelium stains poorly, showing swelling and desquamation throughout. In some areas large casts have separated from the basement membrane. (Figs. 1, 2 and 3.)

PROTOCOL—Q 15. White bull dog weighing 12 kg.

June 22, 1925. Urine free of albumin and casts; specific gravity 1.035. Phthalein excretion, 70 per cent in two hours. Blood nonprotein nitrogen, 29.4 mg.; urea nitrogen, 14 mg.

June 27. Left nephrectomy was done under ether anesthesia. Wound healed *per primum*.

July 1. Urine shows no albumin or casts. Phthalein excretion in two hours, 70 per cent. Blood nonprotein nitrogen, 24.4 mg.; urea nitrogen, 16 mg.

July 2. An area 15 cm. square with right costovertebral angle was exposed to 200 kilovolts with 30 millampères at 50 cm. skin distance and with filtration of 1 mm. of aluminum and 1 mm. of copper for thirty minutes. Four days subsequently the marked change in the blood findings was a urea nitrogen of 23 mg.

July 18. The same dosage of Roentgen ray under similar conditions was given. Following this treatment the output of urine was noticeably increased and the specific gravity averaged 1.010. Many clumped leukocytes and albumin was present.

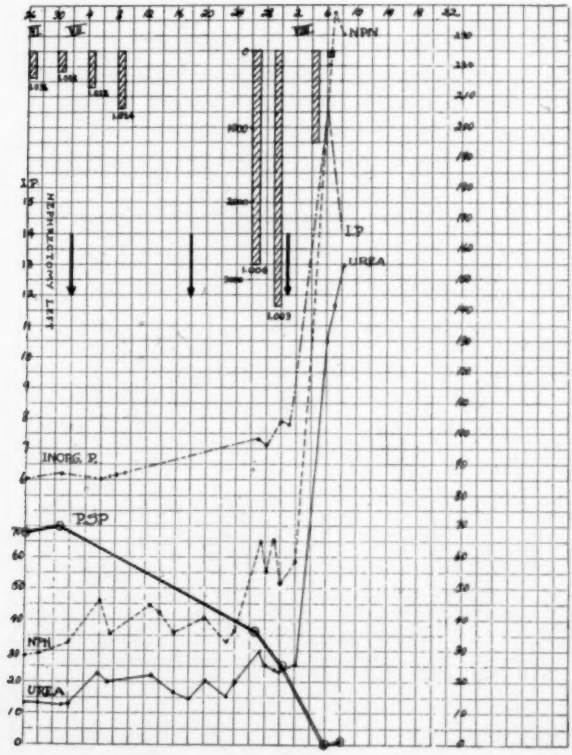


FIG. 6, Q 15.—Composite chart of phthalein excretion, blood nonprotein nitrogen, urea nitrogen and inorganic phosphates throughout the course of the experiment; also the urine output and specific gravity of same as indicated by columns at the top of chart. The arrows represent the Roentgen ray treatments.

July 20. Phthalein excretion in two hours, 36 per cent.

July 27. Urine excretion, 2000 cc. in twenty-four hours. Urea nitrogen of the blood, 30 mg. White blood cells, 22,700. The animal vomits frequently and has little appetite.

July 31. A third irradiation similar in dosage to the previous two was administered.

August 6. The animal became comatose and diffuse muscular twitching and grinding of the teeth were noted. Blood nonprotein nitrogen, 230 mg.; urea nitrogen, 120 mg.; phthalein excretion, none; no urine output and no dye excretion in two hours. Calcium chlorid intravenously relieved the tetany and urine excretion started again. The blood chemistry remained the same and the urine excreted showed many leukocytes and 3 gm. of albumin per liter.

August 8. The nitrogen retention persisted. The CO_2 capacity of the plasma was 13 per cent. Phthalein excretion, 1.5 per cent in two hours. Death occurred this date.

Autopsy. Showed nothing remarkable in the intestines or stomach. The remaining right kidney presented multiple abscesses and was only slightly smaller than the left removed at operation (see Fig. 4).

Microscopic. Right Kidney. Outside the areas of intense polymorphonuclear infiltration and hemorrhage the tubules are distorted, widely dilated and in some instances filled with homogeneous blue staining material. The glomeruli are relatively well preserved but the capsule of Bowman is thickened. The left kidney removed surgically shows no marked abnormalities, grossly or microscopically. (Figs. 5 and 6.)

PROTOCOL—C 16. Airedale mongrel weighing 17 kg.

February 1, 1925. Urine specific gravity, 1.039; contains neither albumin or casts. Phthalein excretion, two hours, 74 per cent. Blood nonprotein nitrogen, 35 mg.; urea nitrogen, 15.8 mg.

February 6. An area 10 cm. square over the left costovertebral angle was given 200 kilovolts, 30 ampères at 50 cm. skin distance for thirty minutes. No untoward symptoms resulted.

February 9. A similar application was made over the right side.

February 17. Urine showed trace of albumin; specific gravity 1.036. Blood nonprotein nitrogen, 36 mg.; inorganic phosphates, 6 mg. During the next four months the blood nitrogen remained within the normal range. The phthalein excretion gradually fell to 65 per cent on March 6 and 59 per cent on June 18. The urine showed a few coarsely granular and hyaline casts with albumin almost invariably.

June 22. Left nephrectomy was done under ether anesthesia. There was some thin purulent discharge from the wound but it closed in fourteen days.

June 28. Urine showed 0.5 gm. of albumin per liter along with leukocytes and casts. Phthalein excretion in two hours, 45 per cent. Blood urea nitrogen, 46.7 gm.

July 27. Urine specific gravity 1.020 with large amount of albumin and leukocytes. Phthalein excretion in two hours 38 per cent. Blood nonprotein nitrogen, 100 mg.; urea nitrogen, 80 mg. Blood pressure by auscultation method: systolic, 120 to 140; diastolic, 30 to 40.

August 3. Irradiation of same dosage used previously was given over right side. Temporary improvement was marked (August 6) by phthalein excretion of 45 per cent and blood urea nitrogen of 36 mg.

August 24. Urea nitrogen was again 48 mg. and phthalein 38 per cent.

September 9. Roentgen ray was applied again over right side, using the same dosage as before.

September 11. Double the previous amount of irradiation was given over right kidney area. Blood pressure at this time 158 systolic and 108 diastolic.

September 29. Daily administration of sodium chlorid 10 to 20 gm. by stomach tube was begun. Blood pressure readings: September 30, 182 systolic and 130 diastolic and on October 3, 220 systolic and 140 diastolic. During the resultant diuresis the blood nonprotein nitrogen dropped to 38 mg. and the urea to 24 mg., but the urine contained 2 gm. of albumin per liter.

October 5. Phthalein excretion, 19 per cent in two hours.

October 9. Blood nonprotein nitrogen, 189 mg.; urea nitrogen, 165 mg., chlorids, 400 mg.; creatinine, 6 mg.; inorganic phosphates, 12.5; calcium, 7 mg. and CO_2 combining power, 38.5 per cent. Animal seemed moribund and was bled to death. (Fig. 11.)

Autopsy. Liver and intestines showed nothing remarkable grossly. The spleen weighed 78 gm. but the capsule was smooth and the pulp was of usual consistency. The remaining right kidney was surrounded by a thick, gray, fibrous capsule which stripped readily showing the parenchyma at either pole dotted by small abscesses. The middle third is flat, firm and fibrous, being free of abscesses. (Fig. 7.)

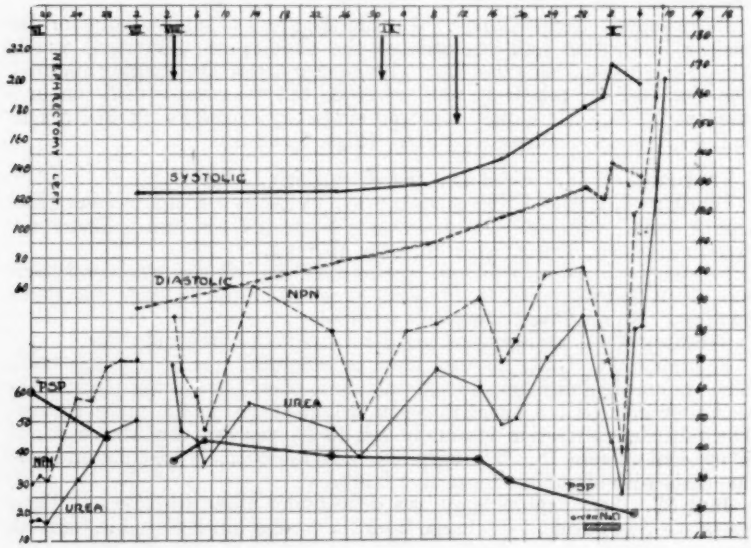


FIG. 11, C 16.—Represents phthalein excretion, blood nonprotein nitrogen, and urea nitrogen along with systolic and diastolic blood pressures. The arrows represent the various treatments and the Roman numerals indicate months.

Microscopic. Right Kidney. The structural changes are largely masked by the polymorphonuclear infiltration but in sections from the middle third the tubules are dilated or compressed and there is a marked increase of fibrous tissue. The bloodvessels are thick walled and the glomeruli are atrophic. Bowman's capsule is thickened and the capsular space contains hyaline thrombi in some cases. (Figs. 8, 9 and 10.)

PROTOCOL—B 13. Large brown mongrel dog weighing 22 kg. Nonprotein nitrogen of the blood, 38 mg. per 100 cc.

August 12, 1924. Received two-hour exposure to 200 kilovolts, 4 milliampères at 50 cm. skin distance over left flank in an area 25 cm. square. Forty cubic centimeters of calcium lactate were injected intravenously after this treatment.

August 15. Animal is vomiting and has diarrhea. It refuses food.

August 20. Appetite good. No further diarrhea.

September 15. Hair is lost from irradiated area. Vomiting after meals is noted.

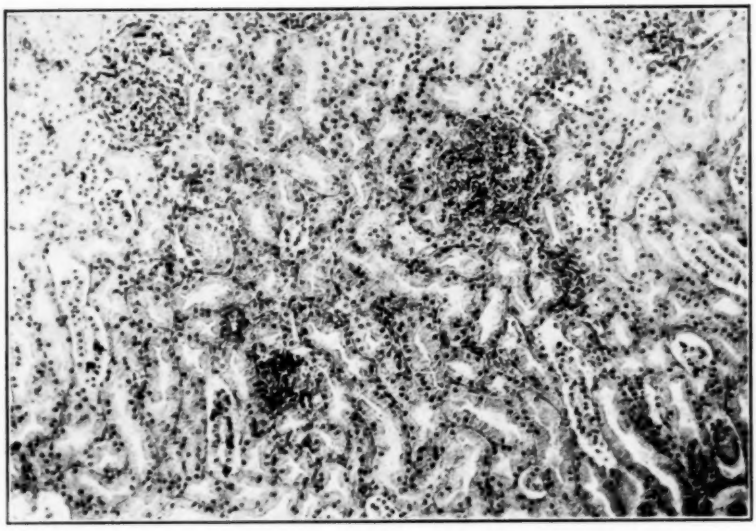


FIG. 1, N 14.—Microphotograph of kidney cortex showing destruction of tubular epithelium with swelling and cellular infiltration of the glomeruli.

FIG. 2, N 14.—High power microphotograph showing destruction of epithelium and epithelial casts.

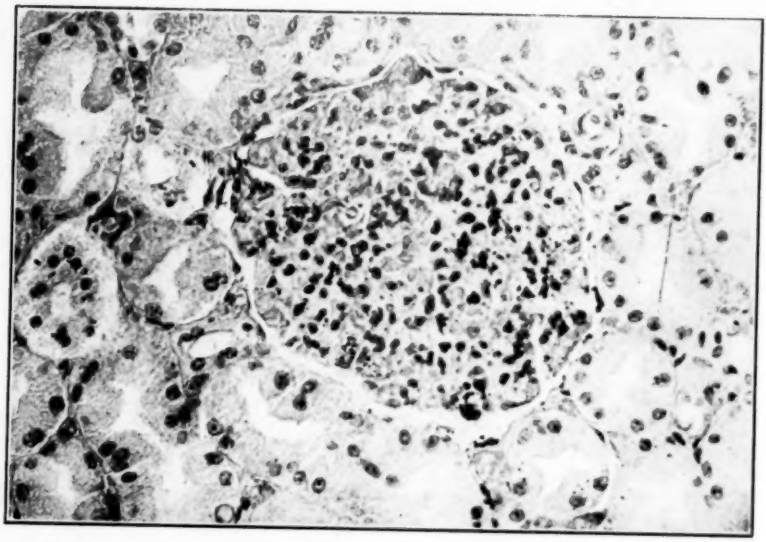


FIG. 3, N 14.—High power microphotograph showing swelling of glomerulus with round- and wandering-cell infiltration.

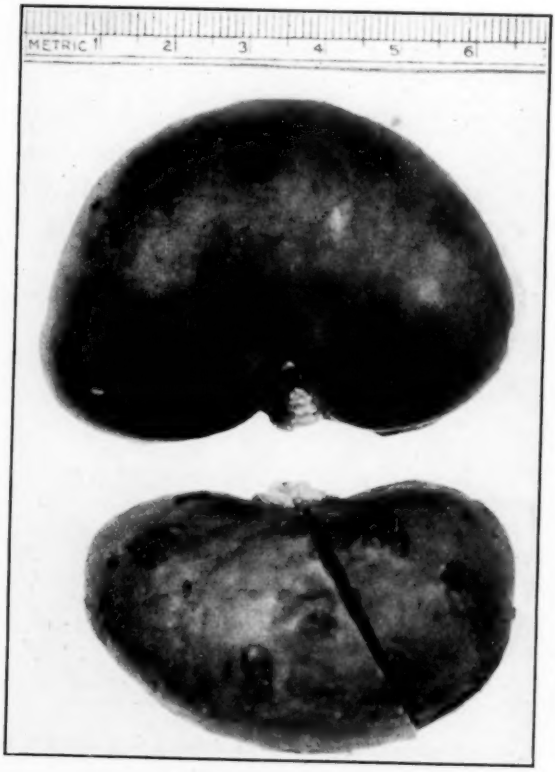


FIG. 4, Q 15.—Showing right and left kidney. The left kidney was removed at surgical operation and is shown in the upper picture. The right kidney (shown in the lower picture) was rayed and shows, in addition to the small size, scarring and the terminal abscess formation.

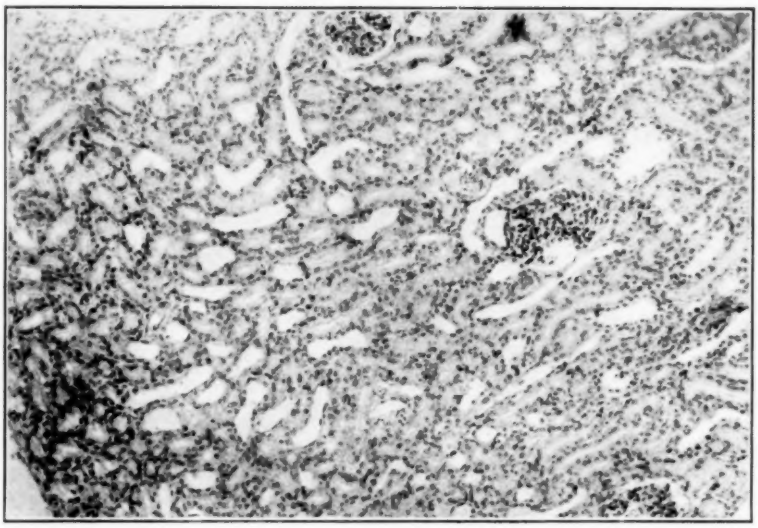


FIG. 5, Q 15.—Cortex of right kidney showing dilated tubules and atrophic glomeruli.

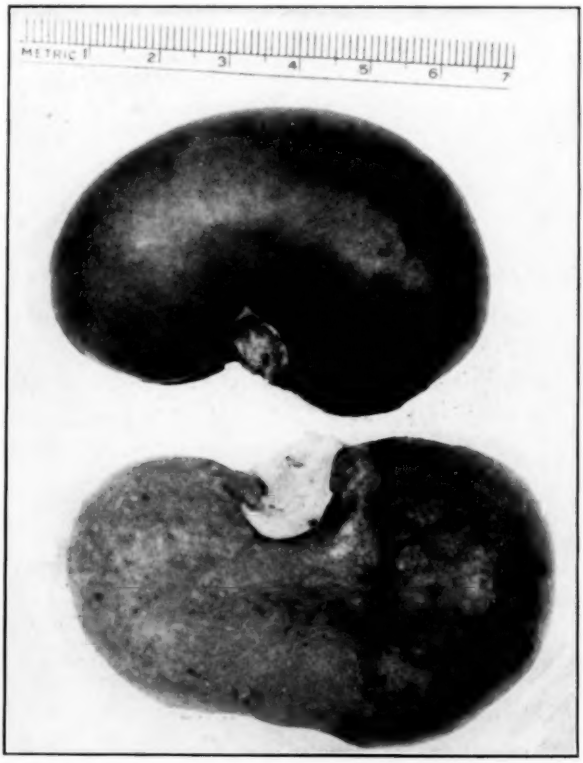


FIG. 7, C 16.—Shows left and right kidneys, the left removed surgically in the upper picture and the lower irradiated showing miliary abscesses in each pole.

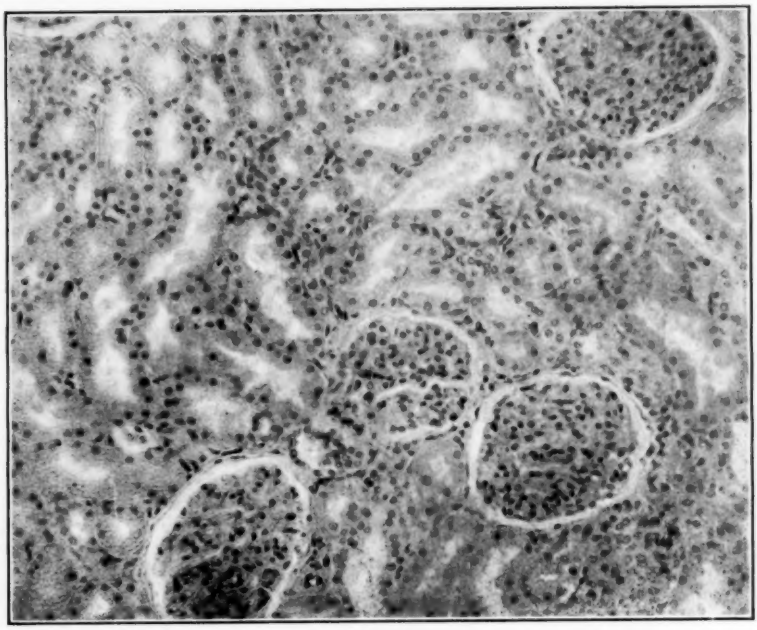


FIG. 8, C 16.—Microphotograph cortex of left kidney removed surgically.

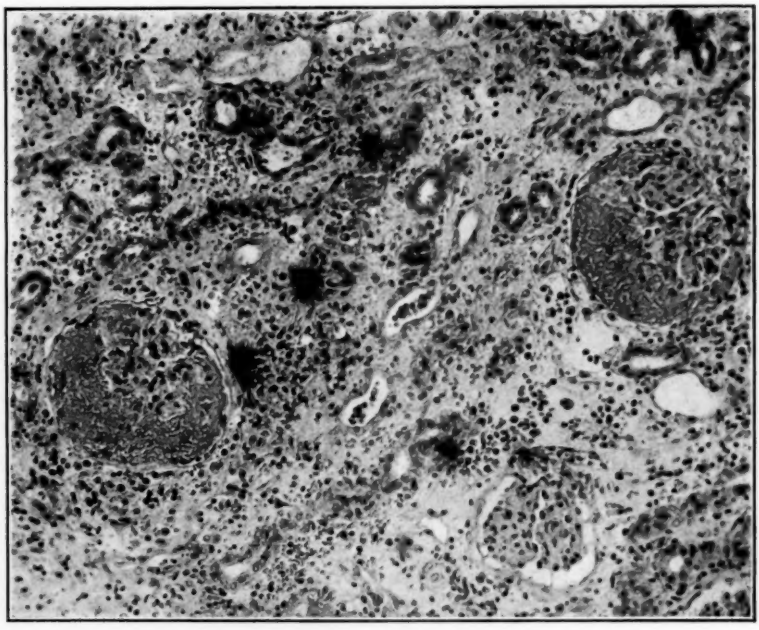


FIG. 9, C 16.—Cortex of right kidney which was irradiated showing distortion and replacement of tubules, atrophy and hyalinization of the glomerular tufts along with a diffuse cellular infiltration.

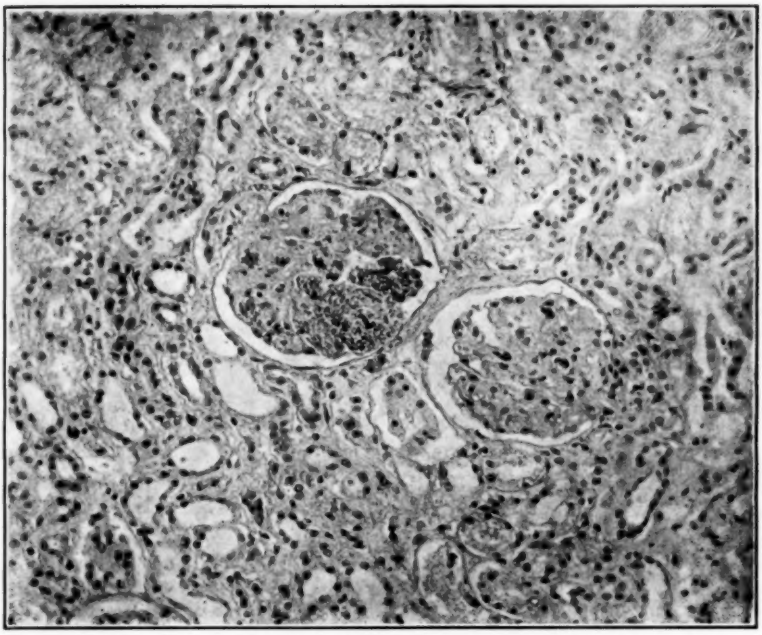


FIG. 10, C 16.—Cortex of irradiated kidney showing atrophic hyalinized glomeruli hemorrhage in one; also dilated tubules.

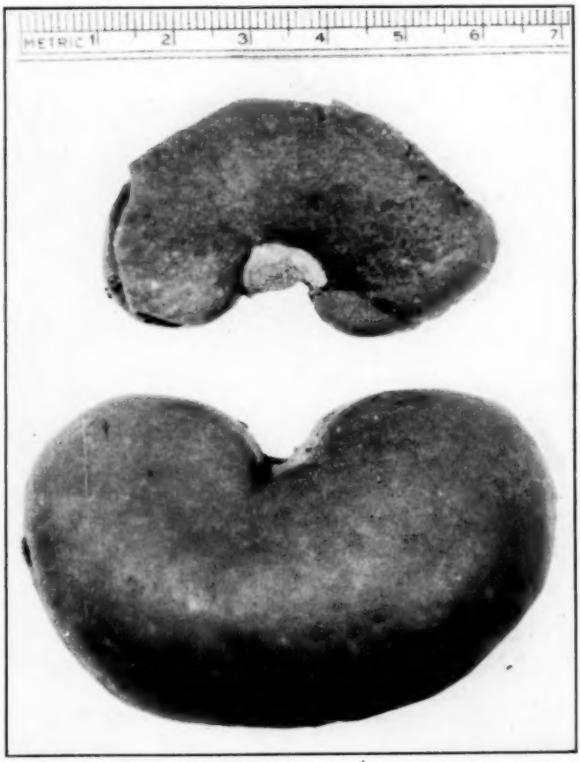


FIG. 12, B 13.—Shows left and right kidneys. The left, in the upper picture, was given a single massive dose of Roentgen ray and the right (in the lower picture) protected as far as possible.

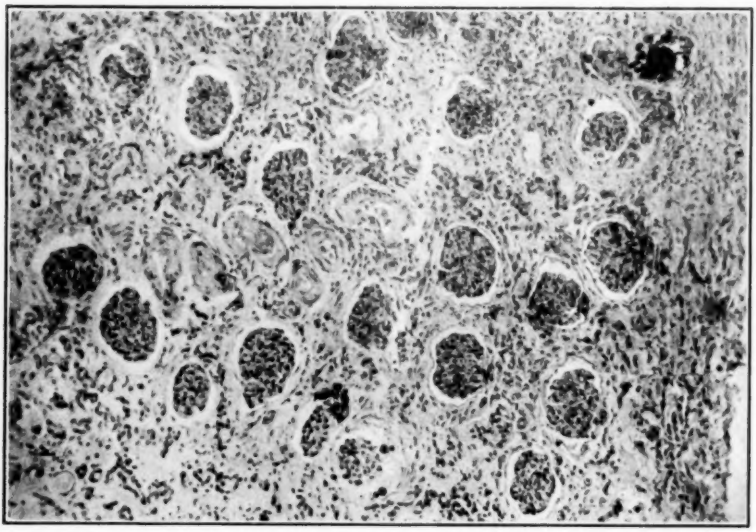


FIG. 13, B 13.—Cortex of irradiated left kidney showing replacement of tubules, atrophy and hyalinization of the glomerular tufts with thickening of Bowman's capsule and in places dark-staining calcium deposits. The bloodvessels are unusually thick-walled.

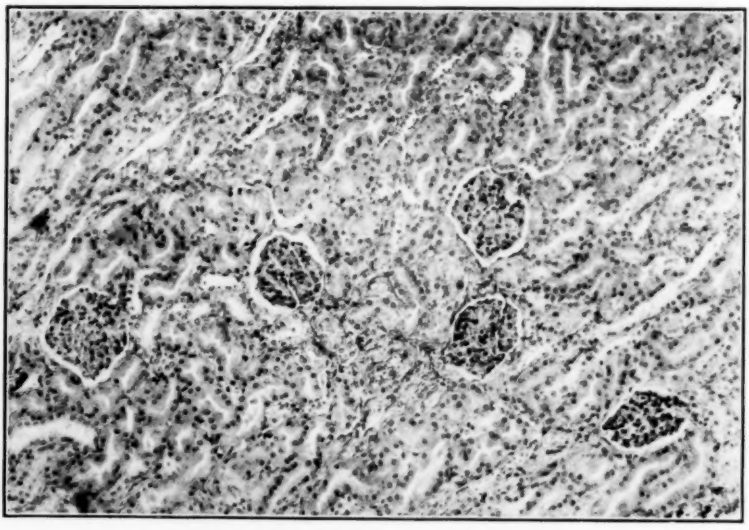


FIG. 14, B 13.—Cortex of protected right kidney showing relatively very few changes.

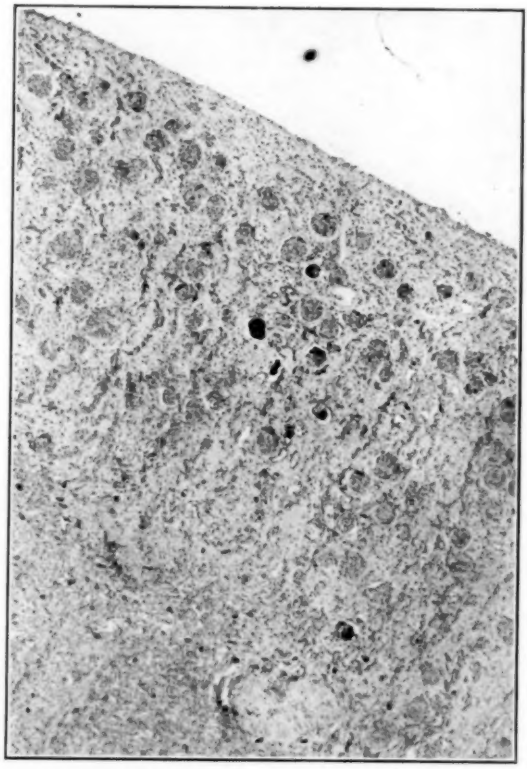


FIG. 15, S 17.—Cortex of right kidney showing replacement of tubules throughout.

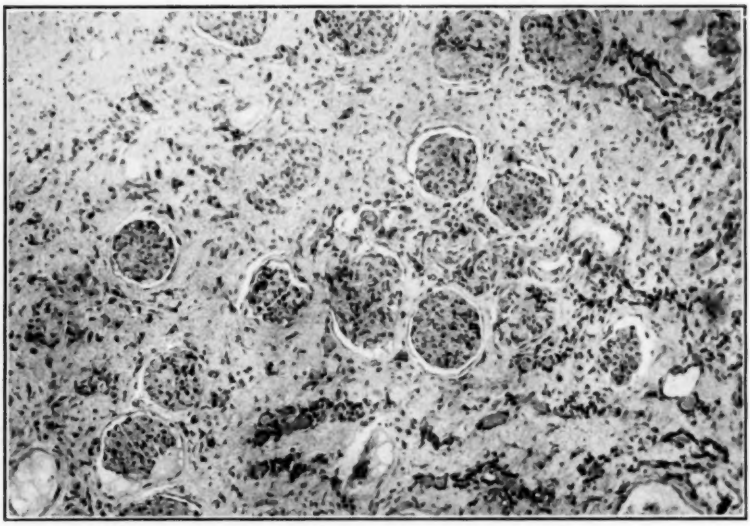


FIG. 16, S 17.—Higher power of cortex left kidney showing replacement of tubules, hyalinization of the glomerular tufts and thickening of Bowman's capsule.

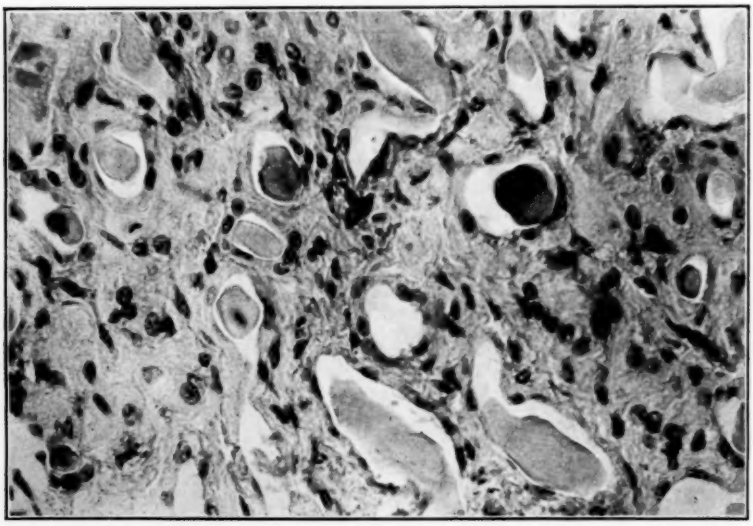


FIG. 17, S 17.—High-power medulla of right kidney showing distorted tubules lined by atrophic epithelium and the lumina filled by homogeneous material.

October 15. Ulceration of irradiated area begins and spreads rapidly, reaching a diameter of 24 cm. in six weeks.

December 18. Urea nitrogen, 23 gm.; nonprotein nitrogen, 43 mg.; red blood cells, 2,950,000; white blood cells, 26,000, with 90 per cent of polymorphonuclears. Autopsy showed extension of the ulceration to the peritoneum with a low-grade diffuse peritonitis. The duodenum and jejunum contain a few oval depressed scars. The adrenals are embedded in dense fibrous tissue but the parenchyma is normally pigmented. The left kidney is one-third the size of the right and weighs 17 gm. It is surrounded by a dense fibrous capsule which strips readily, leaving a roughly granular surface. On section the parenchyma is tough and fibrous, the cortex ranging from 3 to 5 mm. in thickness. Bloodvessels throughout are thick-walled and gape. The cortex is pale and the glomeruli show a marked relative increase in number. The epithelium lining the pelvis is intact. The right kidney is larger than normal. The capsule shows no thickening and strips easily, leaving a smooth unscarred surface. On section the parenchyma is of usual consistency. The cortex ranges from 5 to 8 mm. in thickness and the dots and striæ are readily made out. The pelvis and calyces appear normal. (Fig. 12.)

Microscopic. Left Kidney. The tubules are almost completely replaced by fibrous tissue and those remaining are distorted and lined by flattened epithelium. The glomeruli appear more numerous than normal but are atrophic and hyalinized in many instances. The capsule of Bowman is very thick and sparsely nucleated. Right kidney shows no striking pathologic changes. (Figs. 13 and 14.)

PROTOCOL—S 17. Large, brown, short-haired mongrel, weighing 20 kg.

January 25, 1924. Urine shows no albumin or casts; specific gravity, 1.038; phthalein excretion in two hours 60 per cent. Blood nonprotein nitrogen, 40 mg.; urea nitrogen, 16.2 mg.

January 30. Two hundred kilovolts, 30 ampères at 50 cm. skin distance was given over left costovertebral angle in an area 15 cm. square with filtration by 1 mm. of aluminum and 1 mm. of copper for twenty-five minutes.

February 2. A similar dosage of Roentgen ray was given over the right costovertebral angle.

February 3. Catheterized urine showed a trace of albumin but no casts; phthalein excretion 66 per cent in two hours.

February 9. Urine specific gravity, 1.037; showed trace of albumin; reaction, alkaline. Blood nonprotein nitrogen, 45.6 mg.; urea nitrogen, 15 mg.; inorganic phosphates, 4.18 mg.; CO_2 combining power, 45.7 per cent; red blood cells, 5,600,000; white blood cells, 15,000; hemoglobin, 78 per cent.

February 25. Urine showed few white blood cells and trace of albumin; specific gravity 1.042; phthalein, 70 per cent in two hours. Blood nonprotein nitrogen, 29.7; inorganic phosphates, 4.15; chlorids, 340 mg.

March 13. Urine showed hyaline and granular casts; specific gravity 1.021. Blood nonprotein nitrogen, 23 mg.; CO_2 combining power, 32 per cent. The animal is sleek and well-nourished but continues to gain weight.

June 1. Urine showed macroscopic blood along with large amount of albumin. Blood nonprotein nitrogen, 29 mg.; urea nitrogen, 14 mg.

June 21. Urine contains 0.6 gm. of albumin per liter; gross blood is no longer present. Blood nonprotein nitrogen, 30 mg.; urea nitrogen, 17.7 mg.

June 24. Urine specific gravity, 1.033; contains 1 gm. of albumin per liter. Blood nonprotein nitrogen, 46 mg.; urea nitrogen, 27.6 mg. Blood pressure: systolic, 195; diastolic, 115.

July 13. Urine specific gravity, 1.025; showed large amount of albumin, hyaline and granular casts. Blood nonprotein nitrogen, 33.3 mg.; urea

nitrogen, 14.5 mg.; chlorids, 480 mg. Animal is quite fat and sleek, weighing 32 kg.

July 27. Phthalein excretion in two hours, 55 per cent. Blood nonprotein nitrogen, 29 mg.; urea nitrogen, 13.5 mg.; inorganic phosphates, 4.6 mg. Blood pressure systolic, 155; diastolic, 50.

July 30. Roentgen ray applied over an area 30 cm. square on each side for twenty-five minutes with 200 kilovolts, 30 ampères, 50 cm. skin distance and filtration of 1 mm. of copper and 1 mm. of aluminum.

August 13. Twenty-four-hour specimen of urine only 300 cc.; specific gravity, 1.03. Blood nonprotein nitrogen, 33.3; urea nitrogen, 14.9 mg.; CO_2 combining power, 39.7 per cent. This day animal was delivered of 10 puppies, 9 of which were living.

August 25. Twenty-four-hour specimen of urine, 480 cc.; specific gravity, 1.027; trace of albumin. Blood nonprotein nitrogen, 40.6 mg.; urea nitrogen, 26.2 mg.; chlorids, 490 mg. Blood pressure: systolic, 138; diastolic, 70.

September 10. Phthalein excretion two hours, 60 per cent. Red blood count, 4,800,000; white blood count, 10,200; hemoglobin, 79 per cent. Blood pressure: 140 systolic; 78 diastolic. Blood nonprotein nitrogen, 45 mg.; urea nitrogen, 21.9 mg.; creatinine, 1.3 mg.

October 12. Catheterized specimen of urine shows 20 gm. of albumin per liter with a specific gravity of 1.026. Blood pressure: systolic 180; diastolic, 120.

October 24. Twenty-four-hour specimen of urine, 1000 cc.; specific gravity, 1.018; albumin 10 gm. per liter. Blood pressure: systolic, 200; diastolic, 135. Blood nonprotein nitrogen, 60 mg.; urea nitrogen, 46.7 mg.

October 31. Twenty-four-hour specimen of urine 2200 cc.; specific gravity, 1.017; contains 40 gm. of albumin per liter. Phthalein excretion, 45 per cent in two hours. Blood nonprotein nitrogen, 71.4 mg.; urea nitrogen, 50.9 mg.; creatinine, 1.4 mg.; inorganic phosphates, 5.3 mg.

November 19. Blood nonprotein nitrogen, 120 mg.; urea nitrogen, 82.2 mg.; creatinine, 2.5 mg.; inorganic phosphates, 5.79 mg. Blood pressure: systolic, 230; diastolic, 150.

November 20. Animal placed on diet of bread and water and under this regime the blood nonprotein nitrogen fell to 35 mg. and the urea to 22 mg.

January 4, 1926. Urine shows 40 gm. of albumin per liter. There are numerous white blood cells and gross blood. Blood nonprotein nitrogen, 73 mg.; urea nitrogen, 50 mg. Red blood count, 3,250,000; hemoglobin, 60 per cent; white blood count, 13,330.

February 17. Phthalein excretion, 30 per cent in two hours. Urine shows gross blood and 60 gm. of albumin per liter. Blood pressure: 182 systolic; 128 diastolic. The animal is still well-nourished but shows spasmodic wheezing with evident respiratory effort and vomits frequently.

February 25. CO_2 combining power is 5.1 per cent, and 40 gm. of glucose along with 50 units of insulin were given intravenously. Blood urea nitrogen, 196 mg.; creatinine, 2.5 mg.; chlorids, 400 mg.; sugar, 103 mg.; inorganic phosphates, 434. At this time electrocardiograph showed inverted *T* waves indicating myocardial damage.

March 3. Animal very weak but able to stand on legs. Occasionally shows muscular twitchings. Blood transfusion of 180 cc. was given with some apparent improvement. Urine at this time contains a large amount of albumin but no gross blood. Red blood count, 1,333,000; hemoglobin, 20 per cent; white blood count, 31,500; polymorphonuclears, 81 per cent. There are numerous nucleated red blood cells throughout the smear. Blood nonprotein nitrogen, 252 mg.; urea, 237 mg.; creatinine, 5 mg.; inorganic phosphates, 4.5 mg.; chlorids, 360 mg.; calcium, 14 mg.; sugar, 154 mg.; CO_2 combining power 38.8 per cent; van den Bergh direct—negative; indirect, 3.44. Animal dies with violent vomiting and convulsions. (Fig. 18.)

Autopsy. Body is well-nourished and on section the panniculus is 1.5 cm. in thickness. The fat has distinct lemon-yellow tint. The omentum is free. Peritoneal surfaces are smooth and glistening and there is no excess of fluid in the peritoneal cavity.

Both lungs are air-containing. The pleural surfaces are smooth and glistening. Pericardial sac contains about 5 cc. of clear straw-colored fluid. The heart appears short and broad. Wall of the left ventricle is 1 cm. in thickness and the valves are intact throughout.

Intestines show nothing remarkable except a few depressed scars throughout the mucosa of the duodenum.

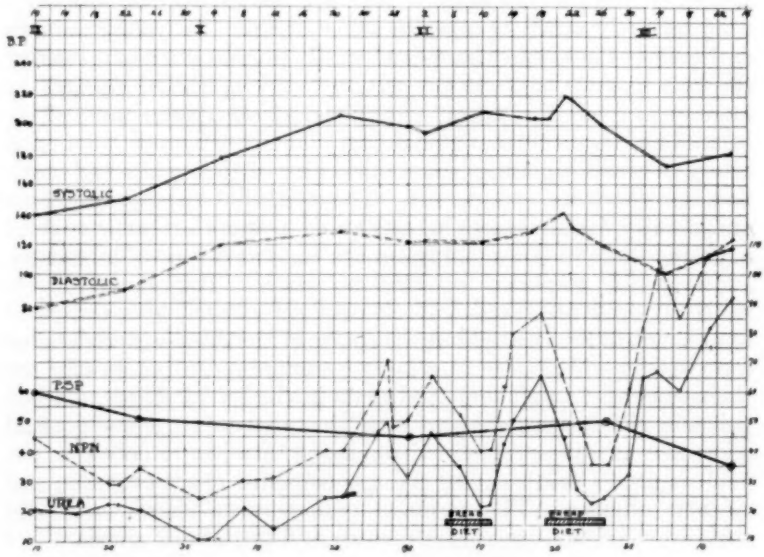


FIG. 18, S 17.—Showing phthalein excretion, blood nonprotein nitrogen, urea nitrogen, systolic and diastolic blood pressures during a three months' period out of a total of fifteen months, during which time this animal was under observation.

The liver weighs 500 gm. It is rather light yellowish-red in color and on section shows a fine nutmeg mottling.

The gall bladder is distended but empties readily.

Spleen is of normal size and consistency except for a grayish-yellow scar in middle third.

Pancreas is somewhat larger than usual and there is some fat necrosis in the adjacent tissues.

The left kidney is of normal size and surrounded by a dense, opaque, fibrous capsule. Capsule strips readily leaving a finely granular surface. On section the cortex ranges from 3 to 5 mm. in thickness and the dots and striæ are made out with difficulty. The pelvis is of normal size and the epithelial lining is smooth. The right kidney is only one-third the size of the left. It is surrounded by a dense fibrous capsule. On section tissue cuts with considerable resistance and the cortex ranges from 2 to 4 mm. in thickness. The glomeruli are seen as numerous small translucent dots but the striæ are not made out. The epithelium lining the pelvis is smooth.

Microscopic. Sections from the left kidney show areas in which the tubules are almost entirely replaced by fibrous tissue. In other areas the epithelium is desquamating and swollen or shows marked vascular degeneration. The glomeruli are relatively well preserved but many of the tufts are atrophic or hyalinized. Capsule of Bowman is thickened in some instances. The right kidney shows more replacement of the tubules and more general involvement of the glomeruli. Many of the tubules which are still intact are filled with homogeneous pink staining material. (Figs. 15, 16 and 17.)

Summary. Renal epithelium is readily damaged by the high voltage Roentgen ray applied through the abdominal wall with comparatively small changes in other organs. In young animals particularly the kidney changes are easily produced without causing the hair to drop out. In proportion to the epithelial damage an increase in interstitial tissue takes place which replaces most of the tubules and distorts those remaining. The bloodvessels from renal artery to small capillaries show thickening of their walls and many undergo complete endarteritis. The epithelial damage gives an opportunity for study of the acute and subacute tubular type of nephritis while the terminal lesion is a combined type of interstitial and vascular nephritis of extreme grade. The glomeruli are relatively well preserved. Work on dogs allowed of satisfactory functional studies throughout the course of the disease, and detailed experiments will appear in a later communication but briefly the changes consist of albumin and casts in the initial stages, marked polyuria with low specific gravity in the subacute stage and gradual depression of dye excretion with marked nitrogen retention in the final stages. Constitutional changes consisted of hypertension and macular changes. The terminal periods were characterized by acidosis, vomiting, convulsions, coma and oliguria or anuria.

NOTE.—Since this paper was presented before the American Society for Experimental Pathology, December, 1925, O'Hare, Altnow, Christian, Calhoun and Sosman have published an article, "Chronic Nephritis Produced by *X*-ray," Boston Medical and Surgical Journal, January, 1926, the work being done on rabbits and using the technic described by Schulz and Hoffmann.

BIBLIOGRAPHY.

1. MacNider: Phys. Rev., 1924, **4**, 595.
2. Allen, Scharf and Lundin: J. Am. Med. Assn., 1925, **85**, 1698.
3. Linser and Baermann: Fortschr. a. d. Geb. d. Rönt., December, 1904.
4. Buschke and Schmidt: Deutsch. med. Wchnschr., 1905, **121**, 495.
5. Warthin, A. S.: AM. J. MED. SCI., 1907, **133**, 736.
6. Schulz and Hoffmann: Deutsch. Ztschr. f. Chir., 1905, **79**, 350.
7. Linser and Helber: Deutsch. Arch. f. klin. med., 1905, **83**, 479.
8. Rosenstern: München med. Wchnschr., 1906, **58**, 1063.
9. Krause and Ziegler: Fortschr. a. d. Geb. d. Röent., 1906, **10**, 126.
10. Hall and Whipple: AM. J. MED. SCI., 1919, **157**, 453.
11. Stephan: Strahlen Therapie, vol. **11**.
12. Martin and Fisher: Am. J. Roentgenol., 1924, **12**, 466.
13. Allen: J. Metab. Res., 1923, **4**, 431.

CONSIDERATIONS OF THE PROBLEM OF BLOOD CLOTTING.

By C. A. Mills,
CINCINNATI, OHIO.

(From the Department of Internal Medicine and the Biochemistry Laboratory, University of Cincinnati Medical College.)

Several theories of blood clotting have for years appeared irreconcilable. Great confusion has prevailed among workers and students of the subject, since some followed one theory and nomenclature and others another. For instance, the remarkably clear-cut work of Howell (1916–1917) on the inhibitors of clotting and the theory he has built thereon have seemed entirely out of harmony with the views of Morawitz (1903), Bordet (1912) and other European workers of note. Wooldridge (1893) had a still different view of the problem.

This state of affairs has, from the first, seemed to us quite deplorable, and it has seemed to be due mainly to a failure on the part of all to place proper emphasis on the work of others. They have, instead, perhaps let their own views of the problem prevent a clear understanding of the work and viewpoint of others. Diligent search has been made in the past two years for a solution of this perplexing problem, one that would harmonize as large a part of the past work on blood clotting as possible. The great bulk of the work that has been done is not to be doubted, but much of its value is wasted in the conflict of theories proposed. We feel now that we can in the main completely harmonize most of the work of Howell with that of Morawitz, Bordet, and so on, also showing how our own past work on tissue fibrinogen, and that of Wooldridge, fit perfectly into a complete picture of the entire process.

This present paper gives as briefly as clarity permits our ideas of the process. The detailed experimental work on which these ideas are based either has been published and is referred to, or else appear in papers now in press.

We are adhering throughout these papers to the term prothrombin as designating the precursor of thrombin, and to cephalin as the name for the agent causing or permitting a thrombin production from the prothrombin of serum. The terms serozyme and cytozyme, respectively, for these two substances seem to us less applicable.

Blood clotting was first studied by us (Mills and others, 1919–1923) from the angle of tissue extract effects. The intense activity of such extracts, especially those of the lung and brain, led us to consider the clotting induced by them as the more truly physiologic clotting, and to picture a defensive mechanism of the body to prevent blood loss, involving this tissue factor and its coagulating action

on blood fibrinogen whenever blood escaped into a wound. No attempt was made during this work to study thrombin clotting, since the tissue extract clotting was believed to be a definitely separate process. We did not hold, however, that tissue fibrinogen clotting explained the whole of blood clotting.

More recently we (Mills and Mathews, 1925) have proven decisively that tissue fibrinogen clotting is independent of thrombin clotting; that the prothrombin of plasma is not used up in such coagulation to any appreciable extent, and, in fact, tissue fibrinogen clotting goes on entirely unhindered in plasma devoid of all thrombin generators. Tissue fibrinogen (containing 40 per cent cephalin, is entirely incapable of activating prothrombin to thrombin, although its cephalin when freed from the protein, is just as active a thrombin producer as cephalin from any other source. For these reasons we hold the two processes of clotting to be independent of each other.

Tissue fibrinogen clotting is pictured as being a truly physiologic process, since it takes place equally well *in vitro* and *in vivo*. The one great objection to accepting the thrombin theories of clotting as physiological has been the failure of thrombin solutions to produce clotting in the vessels when injected directly into the blood. Many repeated attempts have only resulted in failure. We have recently discovered the precautions which, when carefully observed, resulted in giving intravascular thrombin clotting with the same regularity and dispatch as was obtained with tissue extracts. The activated serum (fresh) must be injected within two to three minutes after the activation by fresh cephalin. If this be done death results within one minute, from solid intravascular clotting. If the activated serum be allowed to age a half hour, its toxicity is entirely gone. This, then, establishes thrombin clotting as also a truly physiologic process.

Having in view the two independent mechanisms for clotting blood, and being satisfied that they are both physiological, the question next arises: What is their relation to each other and to the normal clotting of blood? As blood is withdrawn from the blood stream and allowed to clot spontaneously, do both processes go on hand in hand from the first, or does one inititate the clotting, to be joined and aided by the other later? Let us first, however, attempt to settle the question concerning the role of cephalin in thrombin production, whether it is acting to neutralize antithrombin present or to activate prothrombin directly.

The conversion of prothrombin to thrombin and the fate of the thrombin formed will be considered first. Serum, as it stands, loses more and more of its active thrombin, the loss being quite rapid during the first hour. It has usually been thought that this thrombin disappearance represents a conversion to metathrombin which is regarded by Howell as a union between the thrombin and antithrombin. Howell holds that antithrombin, normally present in serum, accounts

for the thrombin disappearance and the failure of all prothrombin to convert to thrombin spontaneously. The addition of cephalin, he says, acts by neutralizing this antithrombin, so that prothrombin conversion proceeds and thrombin destruction stops. Bordet and others, however, assign to cephalin only an action in the direct transformance of prothrombin to thrombin. We have evidence at hand to show conclusively that both views are entirely correct, that is, that there is an antithrombin in normal serum which combines with and is neutralized by cephalin, and also that prothrombin unites with cephalin to be converted to thrombin.

To begin with, we show in another paper (Mills, 1926) that, following cephalin addition to serum about one hour old, from which almost all the thrombin has disappeared, an exceedingly active thrombin generation takes place. Thus far the process might be explained by either of the theories of cephalin action. However, as one watches this activated serum for a time one sees a rapid decline in its thrombic activity until it reaches its former inert state. On the addition of further cephalin at this time one finds a thrombin generation almost equalling that resulting from the first cephalin addition. An amount of cephalin giving the maximum thrombin activity was used each time, so one cannot say that the second addition merely caused the conversion to thrombin of previously undisturbed prothrombin. Following each cephalin addition the thrombin disappearance is always to be observed, although it becomes slower and slower as the cephalin is added time after time.

Now if, as Howell claims, the cephalin acts only by neutralizing the antithrombin, it is rather difficult to explain the effects of repeated cephalin additions as described above, for one can scarcely see how the antithrombin could be neutralized, disappear, and reappear time after time in a given sample of serum. Furthermore, we are led, from the above, to conclude that prothrombin is regenerated from the thrombin as the latter disappears on standing, instead of the thrombin being converted into inactive metathrombin.

This thrombin disintegration and prothrombin regeneration is much hastened, in fact is completed in a few minutes, by the addition of the protein fraction of tissue fibrinogen. This anticoagulant protein exhibits a great avidity for cephalin at all times. No other property of it has been found to account for its anticoagulant action. It is here, then, acting as a true antithrombin, being many times more active than the normal antithrombin of serum. At present we have little doubt that the antithrombin of plasma or serum heated to 60° C., as described by Howell, represents the proteins possessing a cephalin binding capacity similar to the protein of tissue fibrinogen, but of lesser degree. On this basis we would explain the changes in serum following cephalin addition as follows: A combination of cephalin and prothrombin takes place (aided by calcium) producing active thrombin. This union is a loose, dis-

sociable one, striking a permanent equilibrium after a few minutes if the other serum proteins are not present (as we show for purified prothrombin). However, in normal serum the cephalin binding proteins gradually take up any free cephalin into a nondissociable union. The continual dissociation of cephalin from the thrombin and its being bound to the other proteins as indicated soon leaves the prothrombin just as it was before the cephalin addition. Now as the cephalin is repeatedly added, these proteins become more and more saturated so that we see the thrombin destruction becoming less and less. This thrombin disintegration is extremely rapid in peptone serum and in hen serum, bearing out Howell's work on the antithrombin content of those serums.

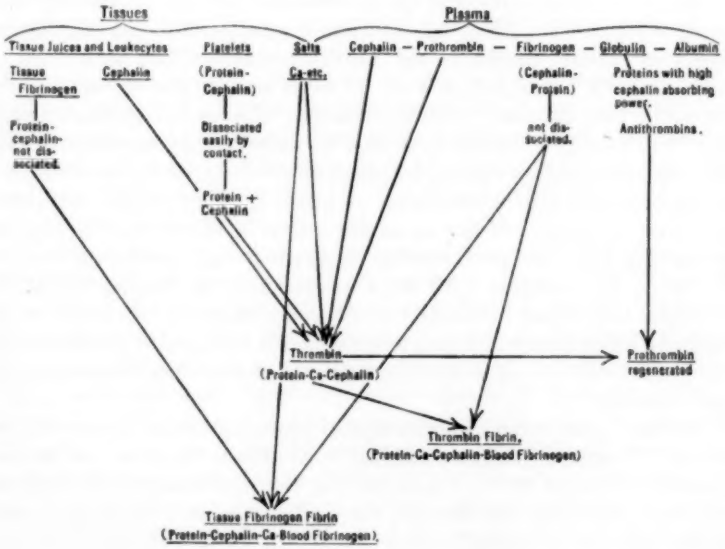
On the basis of the above-mentioned observations, we feel compelled to incorporate both views of cephalin action into our clotting picture. We believe Howell to be quite correct in his demonstration of an antithrombin in plasma and serum, and in his neutralization of it by cephalin. Morawitz, Bordet and others also seem quite justified in asserting that cephalin itself activates prothrombin. (It will be shown in a forthcoming paper that purified prothrombin produces no thrombin whatever on treatment with either calcium or cephalin independently, but goes entirely over into thrombin on treatment with both together.)

This view of thrombin production and destruction in serum, embodying both of the main conflicting theories, we feel to be quite fully justified on the basis of the evidence we are presenting.

There occurs a rather slow loss of prothrombin from normal horse serum kept on ice. This loss is much more rapid at room temperature and is more rapid in some serum samples than in others. The rate of its disappearance roughly parallels the thrombolytic power of the serum. What becomes of this prothrombin has been quite a puzzle. Just recently we have discovered that this disappearance may be greatly hindered and some of the lost prothrombin recovered by adding sufficient solid NaCl to make a 6 per cent solution in the serum. The action of the salt is most likely a dissociating one, similar to the action of an 8 per cent NaCl solution in liberating thrombin from fibrin. One might well conclude that the prothrombin forms a molecular union with the antithrombin proteins of the serum, since its disappearance parallels their activity, and that the NaCl prevents this union, or dissociates it after it has once formed. Whether the cephalin already taken up by these antithrombic proteins is necessary for this binding of prothrombin cannot be said. The resulting compound may well be the metathrombin described by Howell. Further work is necessary before a clear discussion of this point can be had.

It might be well at this point to consider our findings in peptone plasma. Witte peptone in 10 per cent solution injected intravenously into the dog markedly increases the thrombin-destroying

action of the dog's serum, that is, Howell's antithrombin. The same solution of peptone, added to normal dog serum, or any other serum, *in vitro*, very markedly inhibits such thrombin disintegration. Added to dog peptone serum it neutralizes the marked thrombolytic activity found there. On the basis of these facts we conclude that some element of the peptone solution forms a molecular union with the cephalin-absorbing proteins of the serum in such a way as to prevent their taking up cephalin. It must be a molecular type of union of a rather low order of stability since the thrombin disintegration is only markedly slowed, to reach the same degree of completion after a much longer time. On injection of peptone into the circulating blood, this same union takes place, and in an attempt to



restore the disturbed equilibrium an excess of these proteins is thrown out, producing the lessened coagulability of the blood. A slow injection of peptone does not give rise to this excess reaction, as is well known. We feel this to be a true immune reaction, and as such it supplies us with an entrance into the study of immunity from this angle.

Wooldridge was really the first to go deeply into the study of tissue fibrinogen clotting. His untimely death interrupted his efforts to determine the significance of thrombin and its source. We have carried on to conclusion the work on tissue fibrinogen clotting, showing it to be an independent process for clotting the blood, having no direct relationship to thrombin production or action. This

brings us to the question of the possible correlation or interdependence of the two clotting mechanisms.

We may state first that tissue fibrinogen clotting seems in no way dependent on the thrombin factors. The prothrombin of plasma is little disturbed by such clotting, and, furthermore, such clotting occurs equally well whether prothrombin be present or absent.

The union of fibrinogen and preformed thrombin takes place without any reference to other blood constituents. This clotting, and that of tissue fibrinogen, take place intravascularly very readily.

With the *production* of thrombin it is quite different. Apparently *thrombin cannot be produced from prothrombin so long as the blood fibrinogen remains unchanged. Remove the fibrinogen by any means* (tissue fibrinogen clotting, staphylococcus growth in plasma, heating to 56° C., salting out) *and the prothrombin at once is readily converted to thrombin.* Thus, fresh cephalin injected into the circulating blood of rabbits produces no results whatever; but if 1 drop of such cephalin be added to ½ cc. of fresh serum, the thrombin produced in two minutes' time is sufficient to clot the rabbit's blood solidly in twenty to thirty seconds after intravenous injection. Likewise citrated plasma clotted by staphylococcus growth has its intact prothrombin left in a condition in which it is as readily activated as is that of serum. If the blood fibrinogen be removed from plasma by salting out, the prothrombin is again found much more easily activated by cephalin. All these points induced Bordet (1920) to conclude that blood fibrinogen acts as a stabilizer of prothrombin, or that the latter exists as a precursor which is changed to prothrombin (very suceptible to cephalin) on removal of the blood fibrinogen by any measure.

We have now some interesting and important data to add to the above. Citrated plasma clotting in fourteen minutes on simple recalcification (at 40° C.), is clotted by tissue fibrinogen, after recalcification, in about one minute, the serum squeezed out rapidly and added back to an equal volume of the uncalcified citrated plasma. Clotting occurs in less than a half minute.

The total lapse of time from tissue fibrinogen and calcium addition to the completion of the second or thrombin clotting, was less than one-sixth that required for clotting on simple recalcification. Why should not the prothrombin be activated as rapidly in the simple recalcification clotting as in the serum from the tissue fibrinogen clot, since both contained the same concentration of calcium and prothrombin? The only difference lay in the removal of the blood fibrinogen in the second case by the tissue fibrinogen clotting. (It must be remembered that the tissue fibrinogen itself is entirely incapable of activating prothrombin into thrombin.) The removal of the fibrinogen, then, allowed the thrombin production to proceed and give rapid clotting on addition back to the citrated plasma, whereas in the first case the blood fibrinogen held

back the activation process and delayed clotting for fourteen minutes.

Another line of experimentation was tried. Taking the fresh serum from the tissue fibrinogen clotting, one part of it was added back to an equal volume of the citrated plasma, while another part was added to a like volume of the citrated plasma just recalcified. Clotting in the latter plasma occurred in about half the time required by the former. This result strongly suggests that the first case represented a straight clotting of the citrated plasma by the preformed thrombin of the serum added, while in the second case the recalcification allowed the prothrombin of the plasma to be activated as soon as some of it was liberated by the action of the added thrombin in starting the fibrinogen removal. The clotting thus started from the action of the added thrombin alone, but was at once augmented by rapid activation of the prothrombin of the plasma in the presence of the calcium. (One must remember here that this same plasma, on simple recalcification, clotted only after fourteen minutes, whereas it clots under the above condition in a few seconds.) These facts seem to us to point clearly toward the conclusion that blood fibrinogen acts as a stabilizer of prothrombin and that the activation of the latter is permitted to begin only after some of the fibrinogen is removed.

This leads us to the assumption that some other process than thrombin action must initiate the clotting process and begin the removal of the blood fibrinogen. This initiating step we believe to be carried out by tissue fibrinogen in the normal clotting of plasma. It may be recalled that tissue fibrinogen clotting in the vessels occurs with great ease and regularity while thrombin production seems impossible. In order to have intravascular thrombin clotting, the thrombin must be injected preformed. We believe, then, that normal wound clotting is usually begun as a tissue fibrinogen clotting, but that, as soon as the first blood fibrinogen is thus removed, the activation of the prothrombin thus liberated starts, and the two processes go hand-in-hand. Contact with dissociating material (glass, dirt, and so on) may also serve to break the fibrinogen-prothrombin complex, liberating a few molecules of prothrombin for starting off the process.

One may well ask, if cephalin is necessary for prothrombin activation, where does it come from when no cells or tissue juices are present? We have used plasma that has passed through a Berkefeld "V" filter and does not clot on simple recalcification. It contains no free cephalin or tissue fibrinogen, but will clot when either of these two are added together with calcium. Such plasma clotted with tissue fibrinogen (containing only nondissociable cephalin) exhibits a marked thrombin production in the serum. As this serum stands, its thrombin reverts to prothrombin, and again no free cephalin is present. There is no free cephalin present before clotting takes

place, nor a short time afterward. This, together with the behavior of prothrombin in plasma, leads us to the conclusion that, in plasma, there really exists a molecular union of fibrinogen, cephalin and prothrombin (whether of the other blood proteins we cannot say. On removal of fibrinogen the equilibrium is broken and a rapid dissociation takes place. The free cephalin and prothrombin now very readily reassociate (probably including calcium this time) to form thrombin. This unstable association is more slowly broken down again by the serum proteins taking all dissociated cephalin into a nondissociated union with them. Apparently the union of cephalin with prothrombin is of a type much more readily accomplished but of less stability than is that with the other serum proteins, so that in the end the latter compounds win.

The ratio of prothrombin and cephalin to fibrinogen in the plasma is about 5 to 1, so that as the tissue fibrinogen removes one molecule of blood fibrinogen from the complex, five molecules of thrombin form to aid in speeding up the clotting. As these five thrombin molecules, and more tissue fibrinogen further act on more blood fibrinogen, for each molecule of the latter removed five new thrombin molecules are formed. This phase of the process accounts for the progressive acceleration in the rate of fibrin production, and the cumulative character of the reaction. Thus one sees a plasma remain quite limpid until suddenly within a very few seconds it is converted into a solid gel. Ultramicroscopic studies of clotting show a distinct cumulative character also. This we believe to be due to the constantly increasing rate of prothrombin liberation as more and more fibrinogen is removed.

Many readers might find it convenient if the ideas of clotting presented here were given in equational form, as for chemical reactions. We, therefore, submit the following tentative equations.

1. *For tissue fibrinogen clotting.*

$$\left.\begin{matrix}\text{Blood fibrinogen}\\ \text{Cephalin}\\ \text{Prothrombin}\end{matrix}\right\} + Ca + \textit{tissue fibrinogen} \longrightarrow \textit{fibrin, i. e.,}$$

$$\begin{matrix}\text{blood fibrinogen} & & & & \text{prothrombin}\\ | & & & & |\\ \text{Ca} & + & \textit{thrombin, i. e.,} & & \text{Ca}\\ | & & & & |\\ \text{tissue fibrinogen} & & & & \text{cephalin}\end{matrix}$$

2. *For thrombin clotting:*

$$\left.\begin{matrix}\text{Blood fibrinogen}\\ \text{Cephalin}\\ \text{Prothrombin}\end{matrix}\right\} \text{minus } \textit{blood fibrinogen} \text{ (removed as fibrin by thrombin or tissue fibrinogen)} \longrightarrow \textit{cephalin} + \textit{prothrombin.}$$

Cephalin × *prothrombin* × *Ca* ⟷ *thrombin.* This reaction is reversible, the thrombin being very unstable. The antithrombic

proteins take up the cephalin dissociated from the prothrombin union.

$$\textit{Antithrombic proteins} + \textit{cephalin} \longrightarrow \left|\begin{matrix}\text{antithrombin} \\ \text{cephalin}\end{matrix}\right.$$

This reaction is not reversible, so that with this and the preceding reaction going on in the same solution, the cephalin must finally all be bound to the antithrombin. The last reaction is much slower, however, than the preceding one, so that the addition of cephalin to the serum results in thrombin formation at once, this being followed more slowly by the deviation of the cephalin from the thrombin to the serum antithrombin. These ideas are depicted graphically in the accompanying chart.

NOTE.—Since writing the above paper, evidence has come to hand which leads us to the conclusion that the blood antithrombin exists in a combined form in the unclotted plasma, just as does the prothrombin, cephalin and fibrinogen. There is little doubt in our mind that a molecular union exists in the plasma between all these elements, this state being responsible for the plasma stability. Once any dissociating substance be added, or one of the combined elements be removed (as fibrinogen removal by thrombin or tissue fibrinogen), then each of the elements is found free and the typical reactions occur.

In a forthcoming paper on the prothrombin, thrombin and antithrombin of plasma and serum, we shall present the evidence for the above conclusions. We shall show that in serum the effect of the addition of free cephalin is quite transitory, the thrombin formed being gradually disintegrated, while addition of further cephalin again acts as did the first. We must infer that the cephalin added is steadily being bound in some stable form (presumably by the antithrombin). Now if one adds cephalin to citrated plasma no such binding of it occurs so long as the plasma remains unclotted. The accelerating action of such added cephalin is in evidence at any time that the citrated plasma is recalcified and permitted to clot. Its coagulative action remains absolutely unchanged after days of standing in the ice box, while the free cephalin disappears from serum almost completely within an hour. It follows from this that the antithrombic proteins in the plasma must be combined in such fashion as to prevent cephalin binding, such as we see taking place in the serum.

We shall also present evidence which leads us to believe that addition of NaCl to plasma sufficient to give a 6 per cent concentration, or dilution with distilled water, serves to break the molecular unions existing in the plasma and bring into view the specific action of each of the plasma constituents. Thus, although cephalin added to citrated plasma remains free and uncombined, if this same plasma

be treated with NaCl, or diluted with water, the cephalin action gradually disappears.

Dr. Nakamura in a paper soon to be published demonstrates a fact of great importance to us and to all interested in blood clotting. He finds, by dark-field microscopic studies of blood clotting, that pure tissue fibrinogen clotting is in all respects similar to thrombin clotting. He further proves that blood fibrinogen freed of prothrombin (and therefore not coagulated by either calcium or cephalin, or both, in twenty-four hours) will clot in a few minutes on addition of pure tissue fibrinogen and calcium. This should allay all doubt as to there actually existing a second (or tissue fibrinogen) clotting process which is just as much a part of the entire mechanism as is thrombin clotting.

Summary. 1. The main conflicting theories of blood clotting are brought completely into harmony by the data and discussion presented in this and the other papers here referred to.

2. Howell's work on antithrombin is confirmed.

3. The direct activation of prothrombin by cephalin and calcium is substantiated.

4. A complete theory of blood clotting, involving both tissue fibrinogen and thrombin clotting, is presented. It incorporates and harmonizes the best work of the past on this question.

5. The more detailed points may be found summarized in papers following.

BIBLIOGRAPHY.

1. Howell, W. H.: The Harvey Lectures, J. B. Lippincott Co., Philadelphia, 1916–1917, Series XII, 292.
2. Morawitz: Hofmeister's Beiträge, 1903, **4**, 381.
3. Bordet, J., and Delange, L.: Ann. de l'Inst. Pasteur, 1912, **26**, 657.
4. Wooldridge, L. D.: On the Chemistry of the Blood, and other Scientific Papers, London, 1893.
5. Mills, *et. al.;* J. Biol. Chem., 1919, **40**, 425; ibid., 1921, **46**, 135, 167; Am. J. Physiol., 1921, **57**, 395; ibid., 1923, **64**, 160.
6. Mills, C. A., and Mathews, A. P.: Arch. Internat. de Physiol., 1924, **24**, 73.
7. Mills, C. A. Am. J. Physiol., 1926 (in press).
8. Bordet, J.: Ann. de l'Inst. Pasteur, 1920, **34**, 561.

THE INFLUENCE OF VARIOUS FACTORS UPON THE HEMAGGLUTINATION OF RED BLOOD CORPUSCLES.

By Charles C. Higgins, M.D.,
Cleveland Clinic, Cleveland, Ohio.

Although the agglutination phenomenon of red blood corpuscles has been recognized for many years, the various factors influencing it have apparently escaped investigation.

In 1903 and 1905, Landsteiner[1] reported the effects of temperature

as an extraneous factor and concluded that at lower temperatures (6° to 8° C.) the adsorption of heterohemagglutinins was more complete than at higher temperatures (up to 45° C.).

In 1921, Jervell[2] reported a series of experiments in which the effect of temperature was ascertained. He demonstrated: (1) That when tested with isoagglutinins, hemaglutination occurred more rapidly at lower temperatures, that is, the red blood corpuscles showed more pronounced agglutination at lower than at higher temperatures; (2) that the corpuscles adsorb a larger amount of isoagglutinins in a given time at lower temperatures; (3) that agglutinins adsorbed at a lower temperature are partly lost at higher temperatures (above 25° C.).

In 1924, Guthrie and Pessel[3] reported their conclusions which substantiate the reports cited above. These authors also emphasize the importance of temperature in isoagglutinin reactions. They state that at body temperature more isoagglutinins are required than at lower temperatures; and also mention the influence of diluted sera and the necessity of observing the results over a longer period of time.

The effect of this time element is frequently observed in the grouping of blood according to the Moss or Jansky classification. Thus no evidence of agglutination may be present at the end of two or three minutes but in five to ten minutes definite clumping occurs. The effects of other extraneous factors such as defibrination, surface tension and gases have apparently been neglected.

In the work here reported I have verified the effect of temperature and have also investigated the influence of other factors upon isohemagglutination.

I. The Influence of Gases on Isohemagglutination. A suspension of red blood corpuscles was secured by adding three drops of blood to 4 cc. of normal saline solution in a sterile test tube. The serum was obtained by centrifuging several cubic centimeters of blood drawn from the basilic vein. The titer of the sera, which in our series was 1 to 40, was then determined; the influence of oxygen and nitrogen was first determined, using serum which had been subjected to laboratory atmosphere as a control. Throughout the series the age, disease, blood grouping and previous transfusions were recorded. The gas was passed into a tube containing the serum until saturation was produced. One drop of the corpuscle-saline suspension of red blood corpuscles was then added to the saturated serum and the time of the initial appearance of clumping (as evidenced by the microscope) and the degree of agglutination were recorded.

Following this first series the effects of hydrogen, of illuminating gas and of carbon dioxid were determined by a similar procedure. After the influence of the gases upon the isohemagglutination had been determined by saturation of the serum, the effect of saturating the corpuscle suspension was studied in the same manner.

TABLE I.—EFFECT ON HEMAGGLUTINATION OF SATURATION OF SERA WITH AIR, NITROGEN AND OXYGEN.

	Age of patient.	Disease.	Previous transfusions.	Blood grouping.	Time in which agglutination occurred, seconds. Air N. O.	Air.	Nitrogen.	Oxygen.
1	38	Hyperthyroidism	None	II	30–40–40	+++○	++⊕	+△
2	32	Hyperthyroidism	None	III	20–20–30	+++○	++⊕	+△
3	42	Hyperthyroidism	None	III	30–28–40	+++○	++⊕	+△
4	32	Ca. liver	None	IV	40–50–50	++⊕	+++○	+△
5	38	Abscess liver	None	II	22–30–30	+++⊕	++○	+△
6	45	Hyperthyroidism	None	II	35–35–30	+++○	++⊕	+△
7	37	Normal	None	III	40–45–45	+++○	++⊕	+△
8	29	Normal	None	IV	35–38–48	+++△	++⊕	+△
9	27	Normal	None	IV	40–45–45	+++○	++⊕	+△
10	48	Hyperthyroidism	One	II	28–32–38	+++○	++⊕	+△
11	..	Salpingitis	None	II	30–30–32	+++○	++⊕	+△
12	52	Hyperthyroidism	None	III	27–30–32	+++△	++⊕	+△
13	52	Fibroids of uterus	None	II	60–60–62	+++○	++⊕	+△
14	36	Hyperthyroidism	One	III	26–28–27	+++○	++○	+△
15	52	Normal	None	IV	32–40–42	+++○	++⊕	+△
16	39	Normal	None	II	28–30–32	+++○	++⊕	+△
17	..	Hyperthyroidism	None	III	30–32–30	+++△	++⊕	+△
18	..	Normal	None	II	32–28–30			
19	22	Normal	None	II	30–32–34			
20	44	Ca. liver	None	II	28–29–34	+++△	++△	+△
21	..	Hyperthyroidism	None	II	30–42–41	+△	++⊕	+△
22	..	Hyperthyroidism	None	III	20–22–28	+++○	++⊕	+△
23	49	Normal	None	IV	30–32–38	+++○	++⊕	+△
24	51	Normal	None	III	20–22–28	+++△	++⊕	+△
25	39	Goiter	None	II	26–28–30	+++○	++⊕	+△

26	..	.....	None	III	28–29–32	+++○	++⊕	+△
27	29	Normal	None	II	26–28–30			
28	34	Normal	None	II	22–26–27	+++△	++⊕	+△
29	42	Normal	None	III	28–29–32	+++⊕	++⊕	+△
30	35	Hyperthyroidism	None	II	30–30–32	+++⊕	++⊕	+△
31	35	Normal	None	III	28–29–32	+++○	++⊕	+△
32	36	Goiter	None	II	26–30–34	+++○	++⊕	+△
33	42	Normal	None	III	21–21–21	+++○	++⊕	+△
34	27	Hyperthyroidism	None	II	20–26–30	+++○	++	+△
35	37	Hyperthyroidism	None	III	21–22–28	+++○	++	+△
36	28	Normal	None	II	29–30–24	+++○	++⊕	+△
37	24	Normal	None	II	23–28–32	+++○	++⊕	+△
38	..	.....	None	III	14–18–22	+++○	++⊕	+△
39	..	Hyperthyroidism	None	II	18–22–28	+++○	++⊕	+△
40	..	Goiter	None	II	24–26–28	+++○	++⊕	+△
41	29	Goiter	None	III	24–26–30	+++○	++⊕	+△
42	32	Sarcoma jaw	None	IV	24–28–32	+++○	++⊕	+△
43	29	Abscess of neck	None	II	24–26–30	+++○	++⊕	+△
44	32	Ca. stomach	None	II	26–28–29	+++○	++○	+△
45	30	Ca. stomach	None	II	21–28–30	+++○	++⊕	+△
46	32	Goiter	None	III	17–24–29	+++○	++⊕	+△
47	32	Normal	None	III	28–32–36	+++○	++⊕	+△
48	68	Normal	None	II	24–30–32	+++○	++⊕	+△
49	26	Hyperthyroidism	None	II	22–20–16	+++○	++⊕	+△
50	29	Hyperthyroidism	None	II	24–31–36	+++○	++⊕	+△
51	31	Hyperthyroidism	None	II	20–22–38	+++○	++⊕	+△

Cases 10 and 14 had received a previous transfusion.

○—Large clumps.
⊕—Medium clumps.
△—Small clumps.

+++ Maximum clumping.
++ Medium clumping.
+ Minimum clumping.

The results of these groups of experiments may be briefly reported as follows: In testing the influence of nitrogen and oxygen upon hemagglutination, the influence of air was used as a control. The average time in which initial clumping occurred was approximately, in air, 21.1 seconds; when nitrogen was used, 28.3 seconds and with oxygen 32.8 seconds. The maximum degree of clumping occurred in the serum which was exposed to the air, the next degree in the serum saturated with nitrogen and the minimum degree in the serum saturated with oxygen (Table I).

In a second series, the effects of hydrogen, of carbon dioxid and of illuminating gas were observed. In this series macroscopic determinations were made.

With hydrogen, the initial appearance of agglutination occurred in 42.7 seconds whereas it occurred in from 45 to 47 seconds in the control exposed to air; moreover the degree of clumping was greater in the former instance.

In the series in which carbon dioxid was used, agglutination occurred in 43.3 seconds and in the controls exposed to air it occurred in 41.2 seconds; the degree of clumping being greater in the control.

With illuminating gas clumping was first observed in 43.7 seconds while in the control it occurred in 31.6 seconds and the degree of agglutination was greater in the control.

When the corpuscle suspension was saturated with gas and the normal serum was used, practically no differences were observed either in the time of the initial appearance of agglutination or in the relative degrees of clumping in the serum exposed to gas and in the control.

II. Effect of Temperature upon Isohemagglutination. Variation in temperature is an important factor in isohemagglutination. By means of an electric heater the temperature was raised from 37 to 50° and the effect upon agglutination was noted. It was found that as the temperature was elevated the time before agglutination appeared was lengthened. At a temperature of 39.5° agglutination was evident in 29.3 seconds while it appeared in 22.3 seconds in the control at a temperature of 37.5°; moreover the degree of agglutination was greater in the control (Table II). At a temperature of 50° agglutination first appeared in 38.6 seconds (Table III).

Directly opposite results were obtained in a similar series which were subjected to lower temperatures. As the temperature was lowered the period before clumping occurred became shorter. At freezing temperature, agglutination appeared in 18.6 seconds while in the control at normal room temperature it was present in 27.5 seconds (Table IV).

III. The Effect on Isoagglutination of Gases Combined with a Change in the Temperature. After the experiments already described, nitrogen and oxygen were successively added to sera until saturation occurred. The agglutination appeared (macroscopically) in 37.5 seconds.

TABLE II.—EFFECT OF TEMPERATURE (39.5°) UPON ISOHEMAGGLUTINATION.

	Age of patient.	Disease.	Previous transfusions.	Blood grouping.	Time in seconds.	
					39.50°	Control, 37.50°
1	..	Normal	None	II	26	11
2	38	Hyperthyroidism	None	II	38	20
3	..	Normal	None	II	27	22
4	39	Goiter	None	II	24	18
5	42	Hemorrhoids	None	II	26	21
6	36	Goiter	None	II	28	20
7	..	Normal	None	III	22	18
8	..	Normal	None	II	27	15
9	..	Normal	None	II	19	19
10	39	Goiter	None	III	41	21
11	36	Hyperthyroidism	None	III	29	22
12	..	Normal	None	II	26	35
13	42	Normal	None	II	28	20
14	65	Ca. stomach	None	IV	49	41
15	39	Colloid goiter	None	II	22	29
16	48	Ca. thyroid	None	III	19	31
17	32	Normal	None	III	24	18
18	38	Normal	None	III	41	24
19	40	Goiter	None	II	29	13
20	42	Hyperthyroidism	None	IV	40	24
21	39	Hyperthyroidism	None	IV	28	21
22	37	Hyperthyroidism	None	II	42	34
23	..	Normal	None	III	29	26
24	..	Normal	None	II	44	32
25	..	Normal	None	II	42	27

TABLE III.—EFFECT OF TEMPERATURE (50°) UPON ISOHEMAGGLUTINATION.

	Age of patient.	Disease.	Previous transfusions.	Blood grouping.	Time in seconds.	
					50°	Control, 37.50°
26	29	Goiter	None	IV	42	27
27	27	Hernia	None	IV	34	24
28	30	Hyperthyroidism	None	III	27	18
29	32	Hyperthyroidism	None	III	41	21
30	..	Normal	None	II	39	22
31	..	Normal	None	II	49	16
32	32	Normal	None	II	32	19
33	33	Goiter	None	III	37	24
34	37	Goiter	None	III	41	28
35	35	Hyperthyroidism	None	III	44	29

TABLE IV.—EFFECT OF TEMPERATURE (FREEZING) UPON ISOHEMAGGLUTINATION.

	Age of patient.	Disease.	Previous transfusions.	Blood grouping.	Time in seconds.		Clumping.	
					0°	Control, 37.50° C.	0°	37.50° C.
1	32	Goiter	None	II	22	28	+++○	++⊕
2	36	Normal	None	II	18	24	+++○	++⊕
3	40	Goiter	None	II	26	28	+++○	++⊕
4	..	Normal	None	IV	22	34	+++○	++⊕
5	34	Normal	None	III	16	24	+++○	++⊕
6	30	Cholelithiasis	None	III	18	30	+++○	++⊕
7	26	Nornal	None	II	12	32	+++○	++⊕
8	32	Normal	None	II	14	28	+++○	++⊕
9	38	Normal	None	II	22	26	+++○	++⊕
10	42	Normal	None	IV	18	24	+++○	++⊕
11	32	Goiter	None	II	16	28	+++○	++⊕
12	28	Tuberculous tendon	None	III	18	18	+++○	++⊕
13	30	Goiter	None	II	22	28	+++○	++⊕
14	30	Normal	None	II	20	32	+++○	++⊕

TABLE V.—EFFECT OF TEMPERATURE ON ISOHEMAGGLUTINATION AFTER SATURATION OF SERA WITH AIR, NITROGEN AND OXYGEN.

	Age of patient.	Disease.	Previous transfusions.	Blood grouping.	Time in which agglutination occurred, seconds. Air N. O.	Air.	Nitrogen.	Oxygen.
1	39	Goiter	None	II	32–39–40	+++○	++⊕	+○
2	42	Hyperthyroidism	None	II	38–41–49	+++○	++⊕	+△
3	..	Normal	None	III	29–32–46	+++○	++⊕	+△
4	..	Normal	One	IV	38–50–52	+++△	++○	+⊕
5	..	Normal	None	II	32–38–42	+++○	++○	+△
6	39	Hyperthyroidism	None	II	36–30–51	+++⊕	++⊕	+⊕
7	41	Goiter	None	II	40–42–60	+++○	++⊕	+△
8	42	Goiter	None	IV	39–39–41	+++○	++⊕	+△
9	35	Basedow's disease	None	IV	32–30–48	+++○	++⊕	+△
10	62	Ca. stomach	None	II	42–43–40	+++○	++⊕	+△
11	29	Ulcer stomach	None	II	36–39–41	+++○	++⊕	+△
12	61	Ca. breast	None	III	33–33–40	+++○	++⊕	+△
13	27	Raynaud's disease	None	IV	32–34–41	+++○	++⊕	+△
14	42	Goiter	None	II	29–49–52	+++○	++⊕	+△
15	36	Hyperthyroidism	None	III	32–41–56	+++○	++⊕	+△
16	39	Normal	None	III	36–42–50	+++○	++⊕	+△
17	41	Goiter	None	IV	36–42–50	+++○	++⊕	+△
18	40	Hyperthyroidism	None	IV	39–46–62	+++○	++⊕	+△
*19	33	Goiter	None	II	41–49–60	+++○	++⊕	+△
20	..	Normal	None	II	46–48–48	+++○	++⊕	+△
21	..	Normal	None	II	48–60–64	+++○	++⊕	+△
22	..	Normal	None	III	51–56–22	+++○	++⊕	+△
23	..	Normal	None	II	49–52–50	+++○	++⊕	+△
24	..	Normal	None	IV	60–65–74	+++○	++⊕	+△
25	..	Normal	None	II	42–54–63	+++○	++⊕	+△
26	..	Normal	None	II	49–53–66	+++○	++⊕	+△
27	..	Normal	None	II	48–56–72	+++○	++⊕	+△
28	..	Goiter	None	II	46–57–84	+++○	++⊕	+△
29	40	Goiter	None	II	59–26–40	+++○	++⊕	+△

* The specimens of serum from 19 to 29 inclusive were observed at progressively increasing temperatures.

TABLE VI.—EFFECT OF DILUTION UPON ISOHEMAGGLUTINATION.

	Age of patient.	Disease.	Previous transfusions.	Blood grouping.	Time in seconds, dilution.		Normal.
					1–10	1–30	
1	32	Goiter	None	II	24	26	18
2	48	Goiter	None	II	16	16	16
3	..	Normal	None	II	30	30	18
4	..	Normal	None	III	29	38	22
5	..	Normal	None	IV	32	40	22
6	27	Hyperthyroidism	None	IV	24	32	20
7	30	Tuberculous hand	None	II	28	32	22
8	34	Normal	None	II	26	29	18
9	19	Hyperthyroidism	None	II	28	20	26
10	55	Fibroids of uterus	None	II	20	28	20
11	66	Salpingitis	None	II	26	32	24
12	29	Normal	None	III	32	36	28
13	..	Fibroids of uterus	None	II	24	30	20
14	24	Normal	None	II	20	24	22

In this series, clumping appeared in the serum exposed to the air in 39.2 seconds; in the serum saturated with nitrogen, in 43.2 seconds; and in the serum saturated with oxygen, in 52.1 seconds. The rapidity with which agglutination appeared was in inverse relation to the elevation of the temperature (Table V).

IV. The Effect of Dilution of Serum. After the preceding tests the serum was diluted with saline solution in the following proportions: 1 to 10; 1 to 20; 1 to 30 and 1 to 40. These dilutions together with a control were run simultaneously. In the control clumping appeared in 20.1 seconds, while in the dilutions listed above agglutination was first observed in 23.6, 27.9 and 31.6 seconds respectively. The degree of agglutination was in inverse proportion to the degree of dilution (Table VI).

V. Effect of Defibrination. Ten cubic centimeters of blood were drawn from the basilic vein and defibrinated; two drops of the defibrinated blood were added to 2 cc. of saline as a control. A slight delay in the appearance of agglutination was noted in the defibrinated blood but the degree of agglutination was similar to that observed in the control. Clumping appeared in the control in 38.9 seconds and in the defibrinated specimen in 40.6 seconds.

Conclusions. Hemagglutination *in vitro* is influenced by various factors. Change in temperature has perhaps the most marked effect.

In the grouping of blood samples the temperature of the room should not be excessively elevated, as clumping is delayed.

Various gases have a definite effect on hemagglutination, either prolonging it or tending to hasten the process.

REFERENCES.

1. Landsteiner, K.: See Guthrie, C. G., and Pessel, J. F.: Bull. Johns Hopkins Hosp., 1924, **35**, 33.
2. Jervell, F.: J. Immunology, 1921, **6**, 445.
3. Guthrie, C. G., and Pessel, J. F.: Loc. cit., 33, 81, 126.

LEUKEMOID BLOOD PICTURES IN VARIOUS CLINICAL CONDITIONS.

By E. B. Krumbhaar, M.D., Ph.D.,
PHILADELPHIA.

(From the Laboratory of Clinical Pathology of the Philadelphia General Hospital.)

Study of the number and kinds of leukocytes in the blood, that from the mere hematologic examination alone may be indistinguishable from one or another of the various types of leukemia, determines two categories: (1) Those that present a real difficulty in

diagnosis from leukemia; (2) those that have a hematologic similarity only. Both are included in this series: The first group, which will receive more detailed attention as obviously of diagnostic importance; the second for the light it throws on the question of leukogenesis. Recent studies in leukemia, while properly enlarging the field included by the various manifestations of this group of diseases, have added to diagnostic difficulties by the recognition of many acute cases which have only a mild leukocytosis, or even a leukopenia, coupled with fever and some localized signs of infections which may make immediate diagnosis a difficult or impossible feat.

Of the several conditions that produce blood pictures that might be confused with leukemia, infectious mononucleosis (with its acute mild febrile course, adenopathy and a leukocystosis due to mononuclears) has received considerable attention elsewhere (Sprunt and Evans,[1] Longcope,[2] Cross,[3] Landon,[4] Pepper[5] and others) and will not be considered further at this point. Landon, incidentally, also pointed out in his paper how a fatal miliary tuberculosis may produce a leukocytosis with mononuclears, reaching as high as 95 per cent.

The present study is based on 10 cases which can be roughly grouped as follows: (*a*) Measles and pertussis, superficially resembling lymphatic leukemia; (*b*) acute infection with lymphocytosis; (*c*) 2 cases of acute infection with hemorrhage, superficially resembling myeloid leukemia; (*d*) terminal septicemia, also with a blood picture resembling myeloid leukemia; (*e*) bone-marrow intoxication (mustard-gas poisoning), with a terminal blood picture like that of acute myeloid leukemia; (*f*) agranulocytosis, offering some diagnostic resemblance to acute leukopenic leukemia; (*g*) myeloma, diagnosed from acute leukemia at the autopsy table only; (*h*) 2 cases with a terminal leukemia blood picture, in which even postmortem examinations could not definitely distinguish between acute leukemia and acute gastrocolitis and Banti's disease respectively.

Group A. Measles and Pertussis. Case I.—I. M., a girl, aged three years, was admitted to the Philadelphia General Hospital, July 20, 1922, for gonorrheal vaginitis. After having been treated for several months, in the course of routine examinations she was found to have a leukocytosis of 71,600, of which 82 per cent were small lymphocytes, of the kind normally found in the blood. If it were not for an earlier leukocyte count of 11,700, the picture of chronic lymphatic leukemia would have been strongly suggested. Ten days later, however, she developed measles and three weeks after that pertussis, which ran a typical course. On February 27, three months after the high count, her leukocytes had dropped to 13,700 with 42.5 per cent lymphocytosis, and as far as known she has had no further trouble.

Discussion. Although it is known that both measles and pertussis may cause a marked relative and absolute lymphocytosis,

this case is unusual both on account of the height of the lymphocyte count and because no other signs of the disease were apparent for ten days. It is surpassed in degree, however, by Bourne and Scott's[6] case of whooping cough which had a leukocyte count of 176,000 (66 per cent lymphocytes) two weeks after onset of infection, and by Cabot's[7] case of pneumonia complicating whooping cough with 94,000 leukocytes (75 per cent lymphocytes).

TABLE I.—MEASLES AND PERTUSSIS.

Date.	Leukocytes.	Polymorphonuclears, per cent.	Lymphocytes, per cent.	Mononuclears, per cent.	Eosinophils, per cent.	Hemoglobin, per cent.	Red blood cells.
Mar. 13, 1922	11,700	84	12.0	3.0	1	68	3,620,000
Nov. 20, 1922	71,600	12	82.0	1.0	5		
Feb. 17, 1923	13,700	51	42.5	1.5	4		

Group B. Acute Infection with Lymphocytosis. CASE II.—E. Q., a young woman admitted to the maternity department of the Philadelphia General Hospital, in May, 1924, further illustrates the difficulty in diagnosing between various conditions with lymphocytosis. On the third day after a normal delivery the patient developed a sudden unexplained fever (102° to 104°) that lasted eight days. This was accompanied by a chill, headache, slight unproductive cough and very vague signs of dullness and distant breath sounds and fremitus in the left axilla, "stitches" in the breast, but no palpable increase in size the lymph nodes. The urine, which had previously been normal, showed albumin and myriads of leukocytes through the febrile attack only. No bacteriologic studies were made.

The leukocyte count of 7600 showed 75 per cent to be lymphocytes; but two days later, with a fall in temperature and improvement in general condition, with a total count of 8500, the lymphocytes had dropped to 30 per cent. Four days later, with a total count of 15,000, the lymphocytes were 25 per cent.

DISCUSSION. In view of the absence of swollen lymph nodes and of the urinary findings coincident with the febrile attack, this was diagnosed as a transient pyelitis with an atypical lymphocytic response to infection, such as described by Cabot.

TABLE II.—ACUTE INFECTION WITH LYMPHOCYTOSIS.

Date.	Leukocytes.	Polymorphonuclears, per cent.	Lymphocytes, per cent.	Atypical lymphocytes, per cent.	Mononuclears, per cent.	Eosinophils, per cent.	Basophils, per cent.	Hemoglobin, per cent.	Red blood cells.
May 24, 1924	7,600	2.5	50	25	17.5	0.84	1.7	73	3,590,000
26	8,500	66.0	30	...	2.0				
30	15,100	74.0	25	...	1.0				

22 per cent of all cells took positive oxydase stain in the first smear.

Group C. Acute Infection with Hemorrhage. CASE III.*—C. S., a white female, aged sixty-one years, was admitted to the Philadelphia General Hospital, anemic, and in a very weak condition, suffering from advanced carcinoma of the breast, with extensive ulceration and hemorrhages. Although she had no signs or symptoms referable to the hemolyto-poietic system (enlargement of spleen, liver, lymph nodes, pains in long bones, etc.) other than anemia, the routine full blood count showed a leukocyte count of 48,000, which two days later rose to 94,500 and the next day to 120,000, the rise in each case being almost entirely due to polymorphonuclear leukocytes. As would be expected with such an extreme rise, many of the polymorphonuclears were immature and somewhat atypical, and a few myelocytes were found in the last two counts.

At autopsy, beside the cancer and a metastatic nodule in the lung, the bone marrow (tibia) was found to be dark brick-red in color, showing histologically an extreme hyperplasia of the various cell types.

DISCUSSION. This case we have regarded as an extreme neutrophilic polymorphonuclear response (the highest that we have been able to find on record) to the combined stimulus of cancer infection and hemorrhage. The evidence absolutely rules out any diagnosis of leukemia, though the extreme stimulus was sufficient to bring immature forms, even myelocytes, into the peripheral circulation.

TABLE III.—ULCERATED BLEEDING CARCINOMA OF BREAST.

Date.	Leukocytes.	Polymorphonuclears, per cent.	Lymphocytes, per cent.	Mononuclears, per cent.	Myelocytes, per cent.	Metamyelocytes, per cent.	Hemoglobin, per cent.	Red blood cells.
June 11, 1923	44,000	95	4	1	...	...	46	
12	94,500	94	2	1	1	2		
13	105,000	96	4					
14	106,000	92	2	2	2	2		
16	120,000	92	2	2	4	...	35	1,860,000

CASE IV.—V. U., a young married woman admitted to the Philadelphia General Hospital on March 4, 1926, showed a leukocytosis of 106,000, of which 27 per cent were myelocytes and myeloblasts. Her hemoglobin was 3.5 gm., and erythrocyte count 1,000,000, a picture quite compatible with that of myeloid leukemia. Inquiry, however, revealed that she had been bleeding for a week following an incomplete abortion and had never previously been affected with any similar trouble. She died the next day, shortly after a transfusion with compatible blood (Group II), and autopsy was refused.

DISCUSSION. These 2 cases illustrate how extreme a leukogenetic stimulus can be produced by hemorrhage, especially if combined with infection. The reason for its potency is not clear, though one of course can think of other examples of nonspecific cellular reaction on the part of the bone marrow. In marked anemias, for

* Reported by C. A. Pons and myself in Studies in Blood Cell Morphology and Function, J. Lab. and Clin. Med., 1924, **10**, 23.

instance, the tissue hyperplasia always includes the leukoblastic elements, to a greater or less extent, as well as the more directly concerned erythroblastic mechanism.

TABLE IV.—ABORTION—HEMORRHAGE.

Date.	Leukocytes.	Polymorphonuclears, per cent.	Lymphocytes, per cent.	Turck cells (2), per cent.	Mononuclears, per cent.	Eosinophils, per cent.	Myeloblasts, per cent.	Myelocytes, per cent.	Metamyelocytes, per cent.	Hemoblobin, gms. p. 100 cc.	Red blood cells.
Mar. 5, 1926	106,000	53.5	7.5	0.5	2.5	0.5	1.5	25.5	8.5	3.5	1,000,000

Group D. Terminal Septicemia. Case V.—M. R., a negress, married, aged twenty-five years, was admitted to the Philadelphia General Hospital, December 28, 1922, very sick, with fever, pain in abdomen and other signs of a pelvic abscess and later developed septicemia (nonhemolytic streptococci and Bacillus coli in blood cultures). Since childhood to the time of the present illness, which began suddenly, five days before admission, the patient had "never been sick." She had several children living, and no miscarriages and her periods were regular.

On January 1, 1923, her leukocyte count was 46,000, of which 83 per cent were polymorphonuclears. On January 4 the count was 112,300 and a differential taken the next day (the day before death) showed 85 per cent polymorphonuclears, 3 per cent lymphocytes and 12 per cent neutrophil myelocytes. Many nucleated erythrocytes were seen and marked polychromatophilia, anisocytosis and poikilocytosis, stippling and occasional mitotic figures. The extremely high total count and numerous myelocytes, together with the marked anemia and structural changes in the red blood cells, might, on the basis of the blood picture alone, easily have led to a mistaken diagnosis of myeloid leukemia. At autopsy (No. 7317), however, not only were no evidences of leukemia to be found, but the tibial bone marrow was found to be fatty and without any visible signs of regeneration. Microscopically also only a very few small clumps of hemopoietic cells were visible. This must be largely discounted, however, by our repeated observations that tibial marrow may be normal while elsewhere (femoral) the marrow is markedly hyperplastic.

Discussion. This case, therefore, emphasizes the fact that in the terminal stages of an acute infection, even without hemorrhage, a blood picture resembling that of leukemia may be produced and that the usually accepted signs of bone-marrow activity in one marrow preparation only do not necessarily indicate a hyperplastic marrow. On account of the prominence of given acute infections in the etiology of acute leukemia, the question also arises whether this might be regarded as a "leukemia acutissima." While this will be considered again in Cases VIII and IX, in the present case, at least, it seems common sense to consider this nothing more than an unusual terminal hemopoietic response to a severe infection.

TABLE V.—PELVIC ABSCESS AND SEPTICEMIA.

Date.	Leukocytes.	Polymorphonuclears, per cent.	Lymphocytes, per cent.	Mononuclears, per cent.	Eosinophils, per cent.	Myelocytes, per cent.	Metamyelocytes, per cent.	Hemoglobin, per cent.	Red blood cells.
Jan. 1, 1923	46,000	83	16.0	1	1	...	...	55	2,300,000
4	112,300	75	6.5	2	1	8	7.5	23	

Group E. Mustard-gas Poisoning. CASE VI.—Pri. H. K.,* gassed May 20, 1918, was admitted to No. 16 General Hospital, B. E. F., with the usual signs of severe mustard-gas poisoning of the face, eyes, arms and legs and, in addition with fever, marked dyspnea, cyanosis and signs of bronchopneumonia. On the eighth day after being gassed he showed the usual leukopenia to an extreme degree, the leukocyte count being 640 per c.mm. (of which 10 per cent were polymorphonuclears and 50 per cent were doubtful mononuclears); the next day the leukocyte count was 520 (with 10 per cent polymorphonuclears and 20 per cent doubtful cells); the tenth day the leukocyte count was 1200 (with 84 per cent myelocytes); the eleventh day (on which he died) the leukocyte count was 5400 (with 91 per cent myelocytes).

At autopsy the femoral bone marrow was unusually pale, with a few small reddish patches at the proximal end only. Histologically, the bone marrow showed some edema and necrosis with deficient regeneration, chiefly primordial cells with few normoblasts, neutrophil and eosinophil myelocytes, some megakaryocytes, phagocytes and extracellular pigment.

DISCUSSION. This case is included, not as bearing any resemblance to leukemia, but as an example of many observed during the war where a severe hemopoietic poison depressed leukogenesis until the body became an easy prey to secondary infection, but where, nevertheless, a terminal supreme bone-marrow effect succeeded in raising the number of leukocytes in the peripheral blood by pouring in immature forms, that is, myelocytes and even myeloblasts.

TABLE VI.—MUSTARD-GAS POISONING.

Date.	Leukocytes.	Polymorphonuclears, per cent.	Lymphocytes, per cent.	Doubtful cells, per cent.	Mononuclears, per cent.	Myelocytes and myeloblasts, per cent.
May 28, 1918	640	10	35	50 (?)	5	
29	520	10	60 (?)	20	10	
30	1200	4	6	2	4	84
31	5400	1	2	1	5	91

* This case was No. 62 in the series reported by me in the J. Am. Med. Assn., 1919, **72**, 39.

Group F. Agranulocytosis. CASE VI.—Ha. I.,* a young married woman, aged twenty-one years, was admitted to the Philadelphia General Hospital, December 29, 1925, with acute gonorrhea and syphilis and both of which diagnoses were amply confirmed by history, examination and laboratory findings. Except for a slight general adenopathy and two carious teeth, there was nothing apparently germane to the present study.

One month later, while her treatment was progressing satisfactorily, her temperature, which had been practically normal, suddenly jumped to 102°, and stayed rather constantly between 102° and 104° for nine days. A superficial ulceration was noted on the gums, which spread during the week and repeatedly yielded smears of Vincent's organisms (though not considered in every way typical). The submaxillary and submental nodes became slightly more enlarged, but the spleen was never palpable. On the eleventh day, the patient never having been more than slightly discommoded, except by the mouth ulcers, the temperature dropped quickly to normal, the ulcers soon healed and the patient has continued well ever since.

TABLE VII.—AGRANULOCYTOSIS.

Date.	Leukocytes.	Polymorphonuclears, per cent.	Lymphocytes, per cent.	Mononuclears, per cent.	Eosinophils, per cent.	Basophils, per cent.	Rieder cells, per cent.	Myeloblasts, per cent.	Myelocytes, per cent.	Metamyelocytes, per cent.	Hemoglobin, per cent.	Red blood cells.
Feb. 2, 1926	15,200	8.0	48.0	..	..	..	..	..	44			
3	4,700	5.0	35.0	..	..	..	..	..	60	..	60	3,700,000
5	4,700	6.0	41.0	..	..	..	..	..	53	..	63	3,550,000
6	3,900	4.0	49.0	..	..	..	..	..	47			
7	5,600	1.0	52.0	3	..	..	..	..	44			
8	4,000	0.5	61.5	3	..	..	..	1	34			
9	3,300											
10	4,000	..	..	..	..	..	..	..	..	..	66	4,030,000
11	6,300	32	55.0	..	..	..	..	..	13			
12	6,000	44	47.0	..	1	..	7	..	1			
13	6,800	40	60.0									
15	6,900	49	46.0	2	2	1	..	..	..	..	98	4,600,000
16	6,100	59	39.0	..	1	1						
18	6,200	52	47.0	1								
22	8,000	65	28.0	5								
Mar. 5, 1926	5,500	56	23.0	5	7	..	6	..	..	2	70	3,400,000
12	5,300	40	44.0	2	3	1	..	..	..	..	80	

Blood examination on the first day of fever showed a leukocyte count of 15,200, of which only 8 per cent were polymorphonuclears, 48 per cent lymphocytes and 44 per cent a doubtful large mononuclear cells which will be discussed further under hematologic considerations and were eventually considered to be myelocytes. The next day the count had dropped to 4700 leukocytes with 60 per cent of the doubtful cells, and during the remainder of the illness the count remained between 3300 and 5600, distributed in a similar manner. On the day on which the temperature dropped, the count rose to 6300 and by the next day the special cells had

* This case will be reported elsewhere in proper detail by Dr. Kotzen, to whom, with Dr. Hurst Maier, I am indebted for the clinical details.

practically disappeared. Although they reappeared later in small numbers, the leukocyte count remained about 6000 and the patient perfectly well until two months later, when she eloped from the hospital.

Discussion. A blood sample taken during the height of the illness was shown to an unusually competent hematologist, who, on the basis of the blood picture coupled with fever and mouth ulcers, was strongly in favor of a diagnosis of acute leukemia. Subsequent clinical and hematologic developments, however, fairly well rules this out, and leave the diagnosis of agranulocytosis (Schultz[8]) as the most probable. Except for the favorable outcome, this case is typical of this newly described condition, and recovery from the first attack is not unknown (Lauter,[9] Moore and Wieder[10]). The leukopenia and the myeloid character of the atypical cells would seem to rule out infectious mononucleosis, though it is not impossible that these two names may eventually be found to represent different forms of the same condition.

Group G. Myeloma. Case VIII.—J. S., a negro, aged fifty-two years, was admitted to the Philadelphia General Hospital, September 14, 1921, complaining of weakness, headache and general pains with a leukocyte count of 19,200, of which 45 per cent were mononuclear cells of various kinds. He had had various diseases of childhood—"malaria" twenty-two years and five years ago and an appendectomy fifteen years ago and he denied venereal infection. A pain in the left flank, referred along the course of the ureter, once was followed by passage of urine containing gold-like dust; and a few nights before admission the urine had stopped suddenly during micturition. The physical examination was practically negative, also the Roentgen ray examination of the spine, sacroiliac joint, gastrointestinal tract and kidney. The urine showed on repeated examination typical Bence-Jones protein in fairly large quantities; also some albumin and hyalin casts. The blood picture (Table X) became more and more suggestive of an acute leukemia with moderate leukocytosis. The monocytes were almost entirely fairly large cells, without much cytoplasm, the somewhat lumpy nucleus containing a darker spot near the center. No granules were seen in the cytoplasm (Wright's stain). Opinion differed as to whether these were atypical early lymphoid or myeloid forms or cells from the myeloma suggested by the Bence-Jones protein in the urine. Unfortunately the oxydase method was not in routine use at that time. Their true nature was only disclosed at autopsy. The patient later complained of pain along the spine and in the hip and grew steadily weaker until death ensued two weeks after admission.

At autopsy (No. 6262, Dr. Hartman, September 29, 1921), besides a moderate chronic interstitial nephritis, myocarditis and arteriosclerosis, there were found peculiar tumors of the ribs and vertebræ, with metastasis to the liver. Smears and section from these areas showed them to be made up almost entirely of a cell similar to that found in increasing numbers in the blood stream. In sections it appeared as a fairly large polyhedral cell, with a round, slightly eccentric, deep-staining nucleus, with heavy chromatin network. The opaque, somewhat lumpy, protoplasm of moderate amount was acidophilic or faintly basophilic in different sections. Similar cells were also found in large numbers in the splenic pulp and between the liver cells and the diagnosis was made of multiple plasma-cell myeloma.

Discussion. This case emphasizes the fact that certain neoplasms of lymphoid or myeloid nature, especially in the terminal stages, may produce a blood picture closely resembling that of one or other of the types of leukemia, especially as Bence-Jones proteinuria has occasionally been reported in leukemia. In fact some writers include both lymphatic and myeloid leukemia among the neoplasms,[11] and even the term "plasma-cell leukemia" has been applied[12] to myeloma with hyperleukocytosis. It seems more reasonable, however, to consider such cases, like the present one and like Lucké's[13] sarcoma that ruptured into the subclavian vein, as examples of tumors that simulate leukemia by discharging their cells into the circulation in large numbers.

TABLE VIII.—MYELOMA.

Date.	Leukocytes.	Polynuclears, per cent.	Lymphocytes, per cent.	Mononuclears, per cent.	Eosinophils, per cent.	Hemoglobin, per cent.	Red blood cells.
Sept. 15, 1921	19,200	55.0	43	2			
16	20,600	36.0	47	16	1.0	60	3,448,000
20*	22,500	35.0	62(?)	3(?)			
23	26,500	20.5	41	35	3.5		
25	31,200	25.0	28	47			

* Five normoblasts, polychromatophilia. In this count obviously many of the abnormal monocytes were included among the lymphocytes.

Group H. Doubtful Leukemia. Case IX.—G. R., a white laborer, aged fifty-two years, was admitted to this hospital with dysphagia, heartburn and gaseous eructations of three months' standing and signs of bronchopneumonia and acute pericarditis. His family history was negative and he had always been fairly well and was able to continue work until the day before admission. He denied excessive use of alcohol and venereal disease. His teeth were in bad shape, breath foul and tongue heavily coated. The abdomen was full and rather flat to percussion, and he occasionally passed some blood in his stools.

His blood count two days after admission showed 20,000 leukocytes, of which 80 per cent were polymorphonuclears; ten days later (the day before death) there were 69,000 leukocytes, which were almost all mononuclears, of a kind to be discussed later. The gastric contents were hypochlorhydric and contained occult blood. The urine constantly showed albumin casts; the blood Wassermann test was negative and the blood urea was 40, creatinin 1.8 and sugar 130 mg.

Two days before death he was given 20 cc. of a 1 per cent solution of mercurochrome intravenously. The possible effect of this treatment on the blood picture must, of course, be considered, though difficult to evaluate.

At autopsy (No. 7627, Dr. McGinnis) the bronchopneumonia and acute pericarditis were confirmed. There was also found cloudy swelling of the viscera, an acute splenic tumor, a pseudomembranous colitis of considerable severity and a hypertrophic gastritis. Although the tibial bone marrow was grossly normal, the femoral marrow was transformed into a gray creamy mass of the consistency of soft cheese. A smear from this marrow disclosed an overwhelming proportion of the same type of cell that was predominant in the last count during life, that is, a large cell with scanty nongranular protoplasm and a large oval vesicular nucleus with well-marked lumps of chromatin. Section showed the marrow to be more

than 90 per cent cellular throughout, due chiefly to these cells. Clumps of the same type of cell were found infiltrated throughout the heart, lung, kidney, liver and adrenal and in the spleen. In the heart they occurred mixed with fibroblasts beneath the endocardium and in large numbers between the muscle fibers, both intravascular and extravascular. In the lung they were found in the alveoli of the consolidated patches in about equal numbers with the erythrocytes in the kidney both in the glomeruli and between the tubules; in the liver, in the capillaries and especially in the portal spaces; in the adrenal between the cortical strands and to a lesser extent in the medulla. In the spleen the normal architecture was largely lost, with homogeneously cellular fields. The same cell predominated (28 per cent positive to oxydase stain), with a scattering of other blood and plasma cells and considerable blood pigment.

Discussion. The postmortem findings in this case would be amply sufficient to warrant a diagnosis of acute myeloid leukemia. The ordinary leukocytosis found on admission, however, and especially in the light of earlier cases of this series, renders this diagnosis less certain and at least limits the disease, if present at all, to a duration of less than ten days. It is, of course, unfortunate that more frequent counts were not made in the interval and in the absence of more definite knowledge about the course of leukemia, positive opinions are impossible; but the possibility must at least be considered that the severe colitis had in this case produced a terminal blood response that closely simulated that of leukemia.

TABLE IX.—DOUBTFUL LEUKEMIA.

Date.	Leukocytes.	Polymorphonuclears, per cent.	Lymphocytes, per cent.	Lymphoblasts, per cent.	Mononuclears, per cent.	Metamyelocytes, per cent.	Myelocytes, per cent.	Myeloblasts, per cent.	Hemoglobin, per cent.	Red blood cells.
April 2, 1923	20,000	80	15	..	5	..	..	..	80	4,930,000
12,	69,000	6	10	55	2	9	13	5	50	2,500,000

Case X.—G. M., white, aged forty-nine years, in 1919 had a slight leukopenia (6600, 5400 and so forth, see Table X), verified on several occasions over two and a half months. For three years he had had a mass in his upper left abdomen, increasing in size and accompanied by general weakness and loss of weight. Iron and arsenic having no effect, he was treated with Roentgen rays irregularly for two years, with decrease and then increase in the size of the mass. In spite of two transfusions he lost ground rapidly, so that on February 19, 1920, the much enlarged spleen and an accessory spleen were removed by Dr. Deaver at the Lankenau Hospital and the liver was found much enlarged. Histologic examination was considered by me to have confirmed the diagnosis of rather early Banti's disease; the picture certainly did not bear any resemblance to that of a leukemic spleen. After a postoperative improvement of a few months the general weakness returned and in June the patient's leukocyte count had risen to 21,200, with 24 per cent polymorphonuclears and 76 per cent mono-

FIG. 1.—Case I. A field showing predominance of mature small lymphocytes. × 1100.

FIG. 2.—Case III. A field showing a myelocyte and young polymorphonuclears (band forms). × 900.

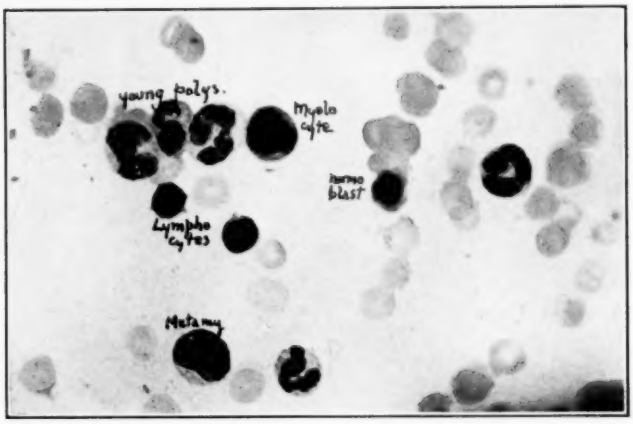


FIG. 3.—Case IV. A field showing many immature cells of the granulocyte series and one normoblast. × 736.

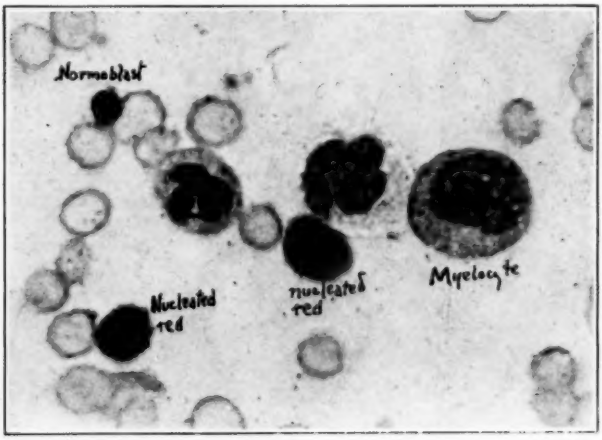
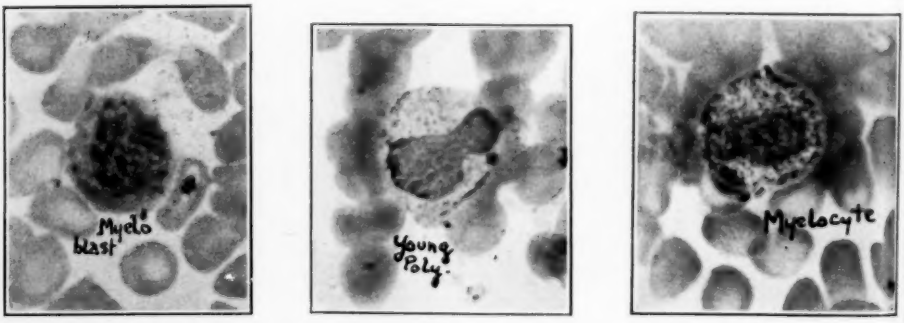
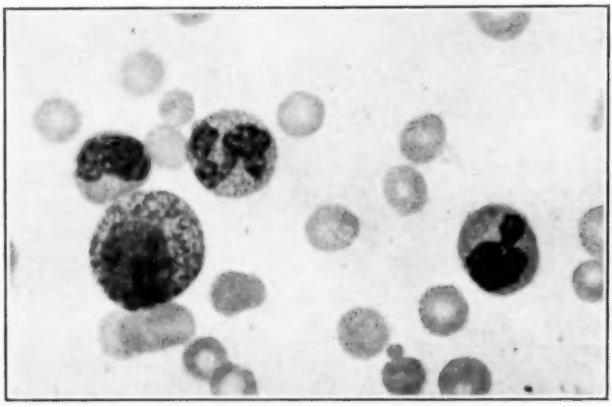


FIG. 4.—Case V. A field showing immature cells of the granulocyte and erythrocyte series. × 1100.



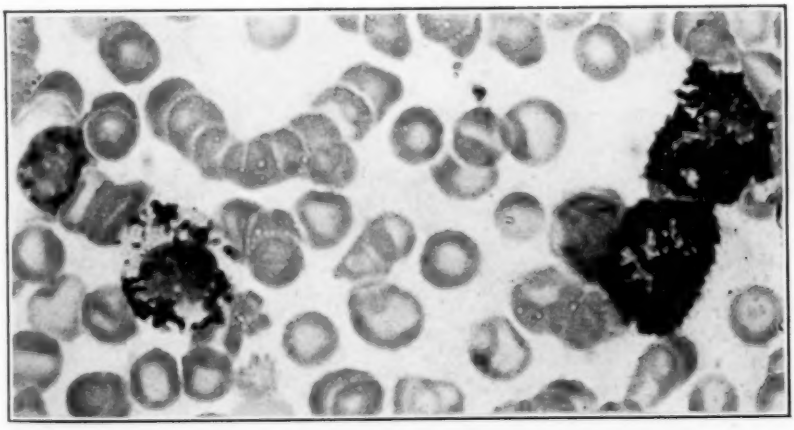
A B C

FIG. 5.—Case VI. *A*, a myeloblast; *B*, a myelocyte; *C*, a young polymorphonuclear (almost a metamyelocyte). × 1200.



A

B



C

FIG. 6.—Case VII. *A*, a field showing immature cells of the granulocyte series, × 1100; *B*, an immature lymphocyte, with faintly basophilic, nongranular protoplasm, × 1200; *C*, oxydase stain, showing two heavily loaded myelocytes, one sparsely loaded myeloblast (?) and one oxydase-free immature lymphocyte, × 1200.

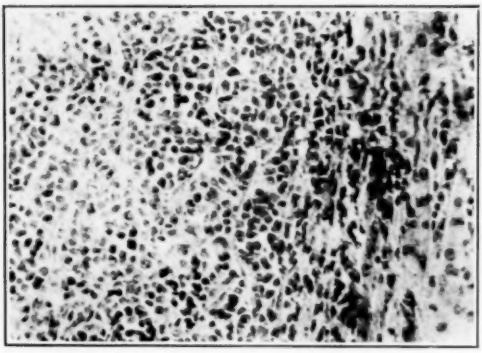


FIG. 7.—Case VIII. Part of a myeloma metastasis in the liver. × 89.

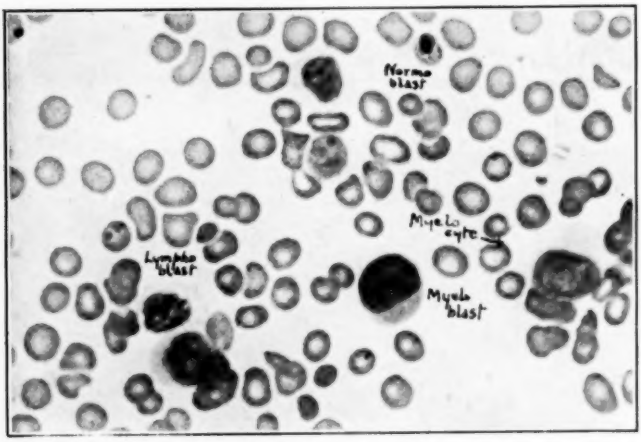


FIG. 8.—Case IX. A field showing immature granulocytes, lymphoblasts and a normoblast. × 736.

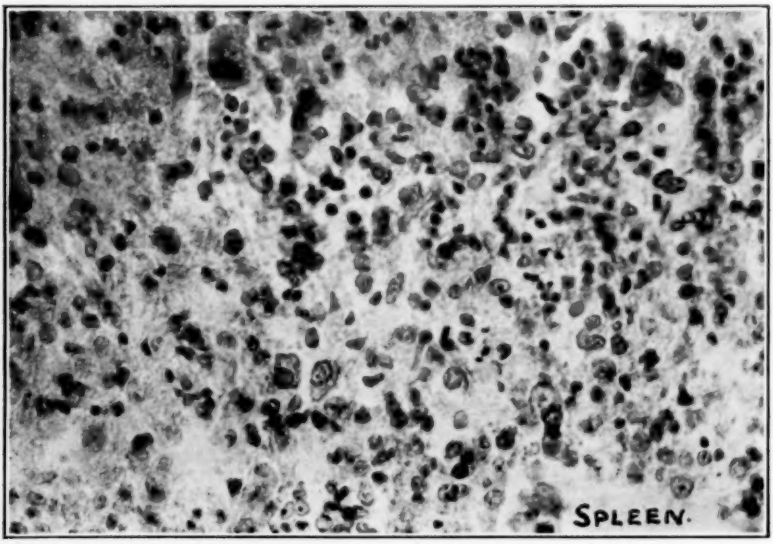


FIG. 9.—Case X. Section of spleen, showing cellular hyperplasia of the pulp, resembling early Banti's disease, rather than leukemia. × 225.

nuclear cells of various kinds. On August 19 he entered the University Hospital and from that time until his death, on October 13, his leukocytes varied from 30,000 to 56,000, with 8 to 59 per cent myelocytes.

At autopsy (Dr. Lucké, University of Pennsylvania, 6837) the liver was found to weigh over 5 kg. and was very pale, with nodules of dirty grayish-brown necrosis. In the lymph sinuses there were many myelocytes. The bone marrow of the right tibia contained a jelly-like gray to grayish-red material, without fat. Histologically, there was an ossifying osteomyelitis and the picture of myeloid leukemia. There were also infiltrated myelocytes in the heart, lungs, liver and pancreas, so that an unqualified pathologic diagnosis of myelogenous leukemia was made.

Discussion. For the first three months this patient's history gave us no ground for objection to a diagnosis of Banti's disease; for the last four it was even more strongly indicative of leukemia. Was it always leukemia, simulating Banti's in an aleukemic early stage, or was it Banti's with a terminal leukemoid picture or was it true Banti's at first merging into a true leukemia at the end? Even continuous study of such a patient would probably have left this question unsolved in the present state of our knowledge of the subject. A few of the pre-splenectomy counts might give rise to some leukemic suspicions, and we do not know what the spleen of leukemia in an aleukemic stage looks like, so that the first of the three suggestions is perhaps nearest the truth.

TABLE X.—BANTI'S DISEASE VS. MYELOGENOUS LEUKEMIA.

Date.	Leukocytes.	Polymorphonuclears, per cent.	Lymphocytes, per cent.	Mononuclears, per cent.	Eosinophils, per cent.	Basophils, per cent.	Myelocytes, per cent.	Hemoglobin, per cent.	Red blood cells.
Dec. 1, 1919	6,600	78	10	12	...	...	...	53	2,640,000
13	5,400	58	30	12	...	...	...	57	2,560,000
21	5,100	60	15	25	...	...	...	50	2,200,000
April 3, 1920	12,550	46	23	31	...	...	...	45	2,210,000
Feb. 11	5,150	54	22	23	1	...	...	45	2,280,000
18	5,300	43	31	26	...	...	...	40	3,310,000
20*									
29	2,700	55	22	23	...	...	...	45	2,140,000
June 10	21,200	24	68	8	...	...	...	60	3,350,000
30	21,200	...	...	...	...	...	...	50	
July 9	20,000	38	62	...	...	...	...	50	
Aug. 6	23,400	7	73	20	...	...	...	60	
19	38,400	44	24	20	2	2	8	45	
23	30,400	47	11	...	1	1	40	47	
Sept. 5	56,900	36	10	2	1	...	51	78	4,260,000
18	52,700	45	3	4	...	...	48	52	3,570,000
21	40,800	37	3	3	...	...	57	51	2,670,000
Oct. 1	42,200	28	16	10	1	1	44	55	3,820,000
13	39,400	48	13	2	...	4	43	65	3,290,000

* Splenectomy.

Hematologic Considerations.—The first 7 of these cases, which are clearly examples of unusual strain being put on one or other relatively normal blood-cell-forming mechanism, illustrate some of the variations in the leukogenetic reactions that may occur. Thus in Case I, in spite of the high figures reached, the cells were of a mature type indistinguishable from the lymphocytes normally seen in the blood.

In Case II, on the other hand, with a mild infection and but slight change in the total leukocyte count, immature lymphocytes of various kinds (lymphoblasts, 1.1 per cent; prolymphocytes, 14.2 per cent; leukocytoid lymphocytes, 5 per cent; Rieder's cells, 6.7 per cent (strumia)) made a transient appearance in the peripheral blood stream.

Cases III, IV and V, all making extreme demands on granulopoiesis, produced in the circulation, as one might expect, granulocytes in the various stages of immaturity in varying degree. In Case III it is remarkable that so few myelocytes appeared, though the more delicate test of the relative number of young and old forms showed a marked increase in the number of the young (metamyelocytes, 2 per cent; band forms, 57 per cent; segmented or thread forms, 41 per cent). In the high count on Case V the myelocytes were somewhat more numerous (12 per cent); whereas in Case IV, not only was the increase in the relative number of young polymorphonuclears more marked (metamyelocytes, 13.7 per cent of all polys; young forms, 58.8 per cent; old forms, 27.4 per cent); but 25.5 per cent of the total count were myelocytes and 1.5 per cent myeloblasts. It would seem as if hemorrhage superimposed on infection and neoplasm was a most potent leukogenetic stimulus and that the longer duration of Case III might indicate a hemopoietic adaptation that accounts for the relative absence of immature forms.

Case VI emphasizes the toxic effect of mustard gas on the hemopoietic system—an observation of ours which has escaped attention in this country (see M. J. Stewart,[14] Warthin and Weller[15]). It seems reasonable to consider that the sequence of events in these cases is about as follows: After an initial irritative leukocytosis (with an Arneth shift to the left, that is, relative increase of young forms); there is a failure in leukogenesis, causing an extreme leukopenia (with gradual Arneth shift to the right). After a week or ten days bone-marrow activity is gradually resumed, and sometimes (as in this case), in response to the extreme demand, immature forms (myelocytes and even myeloblasts) appear in the circulation. This, however, is usually incapable of protecting the patient from the bronchopneumonia which so frequently followed gassing.

In Case VII the changes in the granulocytic cell picture were out of all proportion to the relatively slight illness of the patient. The practical disappearance of recognizable polymorphonuclears from the blood stream is characteristic of this condition (agranulocytosis).

The special cell that appeared in such large percentages (34 to 60 per cent) caused considerable difficulty in classification. With Wright's stain it seemed most like a myelocyte in size and shape, but its granules were small, few and inconspicuous, and seldom found overlying the nucleus. It bore a resemblance to the large mononuclear of the normal blood (though more granular), and as the young and immature forms of lymphocytes also occurred in increased numbers and their cytoplasm showed different staining depths, these also presented difficulties. The Goodpasture oxydase stain, however, showed the great majority to be heavily loaded with oxydase granules, so that most of the unusual cells were finally thought to be atypical myelocytes. A small number of smaller cells with more basophilic cytoplasm and occasional nucleoli were thought to be myeloblasts, especially as the oxydase stain also showed some of this type, with few and widely scattered oxydase granules. Accepting this interpretation of the blood findings, it is striking that such a mild illness and mild leukopenia should have called forth such a number of immature cells and atypical at that. One is reminded of the unusually high reticulocyte count in hemolytic jaundice and is tempted to take refuge in the convenient explanation of a specific toxic effect on the myelocyte in this disease.

The cells of Case VIII need not detain us longer from the hematologic point of view. Though at first their origin was uncertain, they were eventually proved beyond question to be neoplastic in origin (plasma-cell myeloma).

In Case IX the blood picture on the day before death had changed greatly from the ordinary leukocytosis of ten days earlier. With a total leukocyte count of 69,000 only 15 per cent were polymorphonuclears and of these 9 per cent were metamyelocytes, 4 per cent young (band) forms and 2 per cent old (thread) forms. Lymphocytes numbered 10 per cent; monocytes, 2 per cent; a slightly larger mononuclear cell (15 to 20 μ), 55 per cent. It was not possible definitely to place this cell. Its large oval, deeply-stained nucleus (10 to 12 μ) and moderate amount of faintly basophilic agranular cytoplasm suggest a lymphocytic or an extremely young bone-marrow origin and the simultaneous oxydase stain (37 per cent positive) supports this view. The same cell was present in large numbers in the femoral bone-marrow smear, where two or more nuclei could often be made out and also infiltrated through the myocardium, kidney, liver, spleen and adrenal. Also there were 18 per cent myelocytes, so that a diagnosis of myeloblasts would best meet these requirements. These unusual cells did not have the usual appearance of myeloblasts however; furthermore, this would constitute an extremely high percentage for these very immature cells to be present in the blood stream, even when the patient was so near the fatal termination. Certainly it must have been either an extremely intense bone-marrow reaction to infection, or an extremely severe leukemia of the acute myeloblastic type.

In Case X the terminal picture apparently offered no obstacle to a diagnosis of myelogenous leukemia from the hematologic standpoint. Difficulties of interpretation of the sequence of events have already been discussed.

Conclusions.—1. In the 10 cases of this series blood pictures were found, which from the appearance of the blood alone would be indistinguishable from one of the various forms of leukemia. In only three, however, was the clinical diagnosis difficult.

2. Occasional nonspecific acute infections may respond with a lymphocytosis rather than a polynucleosis.

3. Acute infections may be so severe that myelocytes or even myeloblasts may be called into the blood strain in considerable numbers, especially as a terminal event.

4. Hemorrhage added to infection, especially in cases of neoplasm, seems to be a most potent stimulus to leukogenesis. If the stimulus is gradually increased, however, very large total counts can be reached without the appearance of noteworthy immature forms.

5. Inhibition or intoxication of the bone marrow may produce a leukopenia which is followed by the appearance of very immature leukocytic forms in the blood stream.

6. Case VII, agranulocytosis, suggests that certain bone-marrow poisons may cause the appearance of very young forms in the blood stream without marked leukopenia or signs of grave disease.

7. Myeloma may produce a blood picture which is indistinguishable from myeloid leukemia by hematologic criteria.

8. Without better knowledge of the causes of the leukemias, cases associated with infection may be encountered in which definite differential diagnosis is impossible, even after an autopsy has been performed. In other words, it may not be possible to distinguish between a terminal leukemoid blood picture (with bone-marrow hyperplasia and infiltration of viscera) and an acute terminal true leukemia.

9. Case X shows that either leukemia in its aleukemic stage may simulate Banti's disease, even to the gross and histologic appearance of the spleen or that Banti's disease may be followed by leukemia or that it may terminate in an indistinguishable leukemoid picture.

It is a pleasure to thank Drs. Reimann, Stengel and Lucké for the material on Case X, and Drs. A. D. Waltz, C. Pons and the chiefs and interns of the Philadelphia General Hospital for aid in the collection and study of this material.

REFERENCES.

1. Sprunt and Evans: Mononuclear Leukocytosis in Relation to Acute Infections, Johns Hopkins Hosp. Bull., 1920, **31**, 357.

2. Longcope, W. T.: Infectious Mononucleosis, Am. J. Med. Sci., 1922, **164**, 781.

3. Cross, J. G.: Conditions Simulating an Acute Leukemia, Minnesota Med. 1922, **5**, 579.

4. Landon, J. T.: Conditions Simulating Acute Lymphatic Leukemia, Am. J. Med. Sci., 1925, **170**, 37.

5. Pepper, O. H. P., and Schenk, H. P.: Concerning the Confusion between Acute Leukemia and Infectious Mononucleosis, Am. J. Med. Sci., 1926, **171**, 320.

6. Bourne, G., and Scott, J. M.: Pertussis with a Leukocytosis of 176,000, Brit. Med. J., 1922, **1**, 387.

7. Cabot, R. C.: Modern Medicine, Lea & Fabiger, (a text-book) **4**, 676; The Lymphocytosis of Infection, Am. J. Med. Sci., 1913, **145**, 335.

8. Schultz, W.: Ueber eigenartige Halserkrankungen; a, Monozyten Angina, Deutsch. med. Wchnschr., 1922, **48**, 1495.

9. Lauter: Zur Frage der mit Agranulocytose einhergehende Falle von septischer Angina, Med. Klin., 1924, **20**, 1324.

10. Moore, J. A., and Wieder, H. S.: Agranulocytic Angina; Report of a Case with Two Attacks, J. Am. Med. Assn., 1925, **85**, 512.

11. Ewing: Neoplastic Diseases, 2d ed., 1922, p. 348.

12. Gluzinski and Reichenstein: Myeloma und Leucaemia lymphatica plasmocellularis Wien. klin. Wchnschr., 1906, **19**, 336 (quoted by Ewing as of 1905).

13. Lucké, A.: Lymphosarcoma der Achseldruse, embolische Geschwulste der Lungen, Allgemeine Leukemie. Tod., Virchow's Arch. f. path. Anat., 1866, **35**, 524.

14. Stewart, M. J.: Report on Cases of Poisoning by "Mustard Gas" (Dichlor Ethyl Sulphid), with Special Reference to Histologic Changes and to Alterations in the Leukocyte Count, Rept. Chem. Warfare Med. Com. to British Med. Res. Com., 1918, No. 17, p. 26.

15. Warthin, A. S. and Weller, C. V.: The Medical Aspects of Mustard Gas Poisoning, St. Louis, C. V. Mosby Company, 1919.

16. Herz, A.: Infektionen mit leukämischen Blutbild, Wien., klin. Wchnschr 1926, **39**, 835.

THE OCCURRENCE OF ANEMIA IN FOUR GENERATIONS.*

By W. W. G. Maclachlan, M.D.,

and

Florence M. Kline, M.D.,

Pittsburgh, Pa.

(From the Medical Clinic, Mercy Hospital, Pittsburgh, Pa.)

Since Klein, in 1891, reported 3 cases of pernicious anemia in one family, there have been numerous observations recorded dealing with the multiple occurrence of pernicious anemia in family groups. As a rule, the number of cases described has not been great, although Bramwell noted 7 instances of pernicious anemia in two generations. This is the largest number of cases that has been recorded up to the present time. There are many authors who have reported on this phase of the disease (Cabot, Gilbert and Weil, Patek, Willson, Bartlett, Roth, Meulengracht, Levine and Ladd, Gram, von Decostello, Mustelin, Gilford, Matthes, Gulland and Goodall, Schauman). Some of them have emphasized the familial tendency to pernicious anemia while others contended that the heredity factor must be very slight inasmuch as pernicious anemia is so commonly seen as an isolated clinical entity and the small groups

* Read by title, Association of American Physicians, Atlantic City, May, 1926.

in families are so rarely observed. Meulengracht has recently discussed this subject in considerable detail and has indicated the difficulties of proving by statistical means the relation of heredity to pernicious anemia. He believes, however, that such a relation exists.

Probably the first observer to lay particular stress on the occurrence of familial pernicious anemia was Schauman. He has written extensively on this subject having had an unusually wide experience with anemia, particularly that form associated with bothriocephalus infestation. In 1900, Schauman called attention to pernicious anemia occurring in families and some time later he was able to collect 24 instances in which at least 2 cases of pernicious anemia were observed in the same family. He believed that there was an inherited predisposition to pernicious anemia and that this factor bore a most important etiologic relationship to the development of the disease. He admitted that there may be many other influences but that these alone were not sufficient to produce pernicious anemia although in the presence of the constitutional tendency these influences might have considerable importance. He regarded bothriocephalus infestation in this light. Considering the prevalence of bothriocephalus in his community relatively few people developed pernicious anemia even when infested with this tapeworm and he, therefore, concluded that a predisposition to anemia must be present even in the presence of the bothriocephalus in order to develop pernicious anemia. Schauman also called attention to the fact that one often encountered in these families not only pernicious anemia but various forms of secondary anemia. No other author appears to have had an experience comparable to that of Schauman with regard to the amount of material observed and, therefore, his views are of considerable importance. Meulengracht appears to agree with the attitude taken by Schauman. They both refer to the difficulty in speaking of the heredity factor in pernicious anemia as it is so difficult to follow cases through a sufficient number of generations to satisfy the usual laws of heredity. What is true for many other diseases in the human such as obesity, diabetes, arteriosclerosis and others, likely also holds good in pernicious anemia with reference to heredity but it is not so evident. Minot has referred to the fact that there may be a constitutional abnormality, an inherent weakness, which permits a reversion of the hematopoietic functions to a somewhat embryonic type in pernicious anemia.

Schauman pointed out that the lack of careful searching of the family history for other evidences of pernicious anemia was the reason why so few cases were recorded. This would appear to be not unlikely. Another factor that he called attention to was that pernicious anemia very often did not develop until late in life and therefore certain possible cases might never develop as death would be brought about by some other cause prior to this time. The

later development also would tend to favor the dissemination of families and this again would make a study of this character difficult and incomplete. We were impressed in our own series with one of these reasons. Nine years ago one of our cases was under hospital observation for a considerable period of time and the record showed no evidence of the family tendency to pernicious anemia. Last fall a sister of this patient was examined by one of us at an office consultation and on specifically inquiring in some detail as to the family history, the large group of cases to be reported was readily obtained. It is not unlikely that the interest developed in the last few years, especially by Draper, has acted as a stimulus to inquire more carefully into familial diseases. Our own experience would, therefore, seem to confirm Schauman's statement that many of these pernicious anemia groups are missed by failure to adequately obtain all the information pertaining to the family history. On the other hand, however, we must believe that in a disease which is comparatively easy in recognition and which is relatively common, the sporadic occurrence of individual cases is the usual form of this condition. The group of anemia cases that we are reporting is the only instance in our own experience where more than one case was noted in a family although we are by no means sure that more careful investigation in other instances might not also have indicated more than a single occurrence. Our series of cases occurred in a family living in a small town in the northwestern part of Pennsylvania. We have data extending over five generations although the anemia cases are only observed up to the fourth generation. It has not been possible to make observations on many of the members of the later generations due chiefly to the fact that some of the family have scattered and up to the present time have been beyond the scope of this study. We have charted, therefore, in the later generations only those cases that we have observed or that we have had very definite evidence concerning their condition. It is our purpose in the future to gradually fit into the chart as many of the missing members as possible so that eventually a fairly complete record of the fourth and fifth generations will be available.

The members of the family under observation have engaged in various occupations. It is interesting that the family themselves are well aware of the fact that there has been a tendency for many of them to develop an anemia and that this has been the cause of death in not a small number of cases. It is the belief among them that this tendency to anemia was first noted in a male ancestor who died in 1844. Most of the information with reference to the earlier generations has been obtained through Dr. S. M. Davenport of Dubois, Pennsylvania, who has known the family for many years and who has been their physician. Many of the later cases have also been well known to him and it is really through his kindness that we have been able to receive much of our data. Dr. Davenport

informs us that it was well known among physicians in the community that the familial tendency to anemia in this family existed.

We have purposely avoided using the term pernicious anemia in our table on account of the fact that in some of the earlier cases one has not proof that the cause of death was pernicious anemia. On the other hand, however, there is good evidence that these cases died of a condition whose chief sign was an anemia. Further, in the later generations there is proof at the present time that some of the members have anemias of the secondary type, so in order to include all under the same heading we have omitted the word primary or pernicious. We would add, however, with the exception of these secondary anemias, that the cases which have been observed by us together with a few studied accurately elsewhere are all typical forms of pernicious anemia. It would, therefore, appear most probable that it is this type of anemia which has accounted for the fatal disease in this group.

The first generation indicates that one male died at the age of forty-four years after an illness of two or three years, which was characterized by a "deadly pallor." This man died in 1844 and the information was obtained from his grandchild, now a woman, aged sixty-five years, who herself has pernicious anemia and who vouches for the accuracy of this history. She informed us that this was a well-known fact in their family. In itself, this is very flimsy evidence but in viewing it in relation to the other cases to be described we may be justified in saying that this man in all likelihood had an anemia.

The second generation, consisting of seven children, are all known and of these three developed anemia and this anemia was the cause of their death. They were all past middle life. The four remaining members of this generation died from other causes and did not have anemia. Two died in the third decade of what was called tuberculosis, one at the age of sixty years from tuberculosis of the kidney and the other after middle life from blood poisoning. In no one of these cases was anemia apparently a factor, at least, not the type that seemingly was present in the other members. The evidence for this generation comes from our informant of the third generation and from Dr. Davenport. All of these cases were well known although they were not diagnosed pernicious anemia at that time for it was not until the next generation that they were so called. It was observed that these cases had a peculiar yellowish color which has been a characteristic throughout. Another interesting factor occurred in this second generation; the four sons who married chose four sisters from the same family. There is no record of any type of anemia occurring in the family to which the wives belonged. This is definitely known because many members of this family still live in the community. From these four sons the family tree has developed in the third and fourth generations and in view of

this fact it is interesting that their wives are sisters and that these wives came from an apparently anemia-free family. The transmission seemingly occurred through the males. It almost suggests a controlled experiment.

The third generation consists of the families of the four sons who had married the four sisters. In this generation our evidence is more definite as all of the cases, with a single exception, have been observed by Dr. Davenport. We have seen three of them, and these are pernicious anemia, two are living and one died of this disease. We shall consider these families in order.

The second son (second generation) who died of an anemia had eleven children, ten sons and one daughter. Four of the sons are still living and apparently well, showing no evidence of anemia. The youngest of these is fifty-four years of age, and the oldest seventy-five years. The daughter died at middle age of a condition called chronic arthritis. She was definitely not anemic. Four brothers died between the ages of forty and fifty years. All of these had an anemia with a definite yellowish tinge. One of them had difficulty in using his lower limbs, in all probability due to cord involvement. Two showed, in later stages of their illness, edema of the lower extremities. The duration of the illness in each was two or three years. Their physician considered that they showed the typical family anemia which he regarded as pernicious anemia. The two remaining brothers with anemia are still living, one is fifty-nine and the other is fifty-seven years of age. We have observed one of them. He has a typical lemon-yellow tinge to the skin and conjunctiva, a sore mouth, a pale smooth tongue, numbness and tingling in the hands. His blood count shows: Hemoglobin, 27 per cent; red blood cells, 2,720,000; white blood cells, 6000. He has a marked variation in the size of the red cells with many macrocytic forms present. No nucleated red cells were seen. He has a gastric achylia. This man has pernicious anemia, despite the low-color index, and his physician told us that he was quite similar to his brothers who have died.* The remaining brother has recently been a patient in the St. Francis Hospital, Pittsburgh, in the service of Dr. F. B. Utley. He has been diagnosed pernicious anemia on typical grounds, as lemon-yellow color, achylia and anemia. The blood count was: Hemoglobin, 46 per cent; red blood cells, 1,272,000;

* Three months later we had the opportunity of making another examination on the blood of this man. The count was as follows: Hemoglobin, 38 per cent; red cells, 3,300,000; white cells, 7400; color index, 0.5. The blood smears showed irregularity in size and shape of the red cells with no nucleated forms present. The bilirubin of the blood serum was 1.87 milligrams per cent. We consider this figure to be a definite increase over the normal which we regard as being 0.5 milligrams per cent according to our way of interpreting the Anderson Thannhauser method of doing this test. We obtained the interesting information from this patient that he had, in addition to his other symptoms as sore mouth, etc., been bleeding for some little time from hemorrhoids. It is possible that this may have modified the figure of the color index.

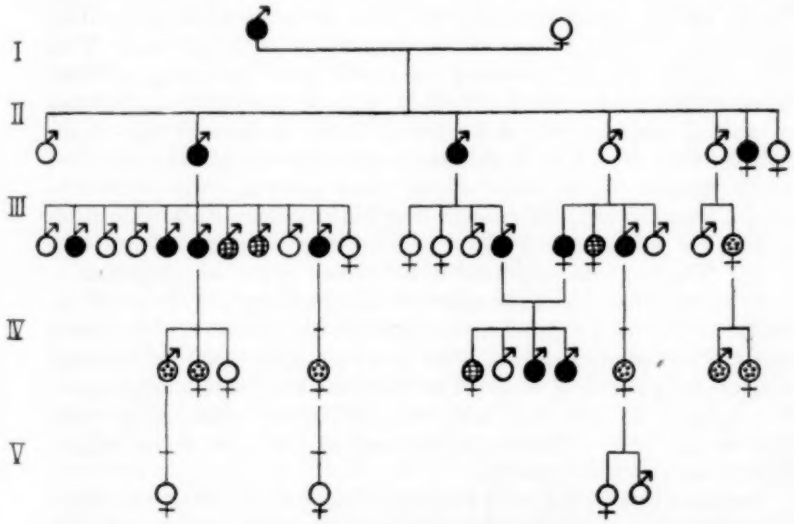
white blood cells, 5000. Numerous macrocytic red cells but no nucleated forms were noted in the blood smears.

The third son (second generation) who also died with an anemia had four children. One daughter died at sixty-five years of age from what was termed old age. She was not anemic. Her sister who is now in the fifth decade is not anemic and is living and well as is also one brother of about the same age. The other brother died at thirty-two years of age of the family anemia. It was diagnosed pernicious anemia by the family physician. He showed signs and symptoms of this condition for a period of about four years.

The fourth son (second generation) did not have an anemia. However, three of his four children showed anemia. One daughter died in the third decade, the immediate cause of death was considered to be pneumonia although she had been suffering for a couple of years from a severe grade of anemia which had been considered to be of the family type and was diagnosed pernicious anemia. Her sister who is now sixty-four years of age is under our observation at the present time. It is from this patient that much of our information has been obtained. She has pernicious anemia, having had symptoms for well over a year. She has numbness and tingling of the hands, an achylia and an anemia. Her blood count shows Hemoglobin, 85 per cent; red blood cells, 3,000,000; white blood cells, 5000. The smear shows many macrocytic forms but no nucleated reds. On several occasions the count has been of about this character. Two observations on the bilirubin of the blood serum showed no increase, 0.5 mg. per cent on one occasion and a figure below this on the other by the Anderson-Tannhauser method. This is the only case of the primary type on which we have been able to do the bilirubin observations as the others have been seen at their home town where it was impossible to carry out the procedure. This patient is the only one who has shown very little of the characteristic yellowish tinge to the skin. One brother died at the age of twenty-two years from an accident. He was not anemic. The other brother died at the age of sixty-two years after going through a typical course of pernicious anemia. This patient we have also seen, he having been in the Mercy Hospital in 1917 in the service of Dr. J. A. Lichty. At that time he was transfused on several occasions. He had a decided yellow-lemon tinge to the skin, the achylia and numbness of extremities. The blood count was always about 2,000,000 cells while in the hospital, in spite of the transfusions. The color index was high, nucleated red cells were never found in his blood, but he had the typical macrocytic picture. We saw him in the following year when he was transfused again. He died about three years after the onset of his symptoms.

The fifth son (second generation) did not have an anemia. He

had two children, a son and a daughter. The son died of general paresis in the fourth decade. He was not anemic. The daughter, aged fifty-three years, is living and apparently well in that she has no symptoms of illness and leads the very active life of a farmer's wife. We have had the opportunity to examine this woman and it is interesting to note that she has a definite secondary anemia as judged from the blood count: Hemoblobin, 59 per cent; red blood cells, 3,860,000; white blood cells, 7000. The blood smear, however, shows no change in the size of the red cells. She had plenty of free hydrochloric acid in the stomach and the bilirubin in the blood serum is below 0.5 mg. per cent. On physical examination we could find no reason for the anemia. She is the first of a group of



DESCRIPTION OF CHART.— ● Died of anemia. ⊕ Living, has pernicious anemia. ◉ Living, has secondary anemia.

secondary anemias, as shown by blood count, that we have noted in this family. This finding tends to confirm the statement that was made by Schauman that the later generations often have secondary anemias in families where the primary type is also seen.

The fourth generation presents some interesting findings. We unfortunately have not been able to make a complete survey of the members of this generation as certain members of the family no longer live in this community and others in this vicinity were not able to be observed at this time. We have charted, therefore, only those that we have seen or concerning whom we have had definite information.

The first group in the fourth generation which we wish to describe consists of three children, a son and two daughters, whose father,

grandfather and great grandfather all died from this family anemia. In the father's case we are certain it was pernicious anemia. Two of these children show evidence of secondary anemia by the blood count. The son, about thirty years of age, showed a hemoglobin of 70 per cent; red blood cells, 3,760,000; white blood cells, 11,000. There was free hydrochloric acid in the stomach. The blood smear appears to be normal. He has no symptoms and appears to be perfectly well. One daughter showed: Hemoglobin, 60 per cent; red blood cells, 4,050,000; white blood cells, 7800. The blood smear from this case showed a tendency toward the development of some large macrocytic forms and the gastric analysis indicated a very small amount of free hydrochloric acid. These observations were repeated in about six weeks with practically the same findings. There was no increase in the bilirubin of the blood serum. This girl is thirty years of age and is apparently perfectly well. This case may be a very interesting one and it is our intention to follow these examinations over a period of years because there is evidence of anemia present with a tendency to the larger red cells while hydrochloric acid is still demonstrable. Her sister who is a few years younger shows no evidence of an anemia. She refused to have a stomach analysis made. The blood picture showed: Hemoglobin, 88 per cent; red blood cells, 4,480,000; white blood cells, 4600. The red cells appeared to be normal in the blood smears.

In another branch of the same group, the daughter of one of the brothers who died with pernicious anemia also showed by the blood count a secondary anemia. She is about forty years of age and appears to be perfectly well. The blood showed the following count: Hemoglobin, 68 per cent; red cells, 3,670,000; white cells, 8000. The smears were of normal appearance and there was free hydrochloric acid in the stomach.

The most interesting of all the groups is the family of four children in the fourth generation whose parents were full cousins and who both died of pernicious anemia. Schauman noted that in the later generations the anemia often appeared earlier in life and was more severe in its type. This group confirms that fact as two of the sons died at the age of thirty-three and thirty-four years of undoubted pernicious anemia. One of them was in the state hospital at Warren, Pennsylvania, and through the kindness of Dr. H. W. Mitchell and I. A. Darling we have been able to get confirmatory evidence of his illness. In several blood examinations that were made one showed: Red cells, 800,000; white cells, 4200; hemoglobin, 16 per cent with a typical smear indicating macrocytes and some nucleated reds. Dr. Davenport has the record of the blood count on the other son taken shortly before death. It showed 910,000 red cells with a typical blood smear. The third son of this family cannot be found at the present time and nothing is known of his condition. The one daughter, aged thirty-five years, presents a very interesting

problem. She informed us that she was perfectly well and indeed her appearance indicated the fact. However, she was very apprehensive about the anemia and probably had good reason to be so. Her blood showed: Hemoglobin, 60 per cent; red cells, 3,390,000; white cells, 8200. The blood smear presented a most decided change in the size and shape of the red cells with many macrocytic cells being present. She had an achylia. We do not see how we can avoid calling this a case of pernicious anemia probably not having advanced to a sufficient degree to produce outstanding symptoms. In this instance, we were not able to make a bilirubin estimation although from the diagnostic point of view, judging from a considerable number of observations in the past three years we are by no means certain that the bilirubin estimation is a valuable as many believe it to be. We have had repeated normal readings in undoubted pernicious anemia. With the exception, therefore, of the boy who is lost, this whole family including parents show pernicious anemia. We are under the impression that later it will be possible to have a record of the absent son.

The daughter of the patient whom we saw nine years ago in 1917, and who died of pernicious anemia, is forty years of age and shows: Hemoglobin, 72 per cent; red cells, 3,560,000; white cells, 5800. She has free hydrochloric acid in the stomach, and the blood smear is normal. Apparently, this woman is well.

The last 2 cases indicating secondary anemia were in the children, a son and daughter, of the woman who showed a secondary anemia in the third generation. It will be seen that in this branch of the family there has been no pernicious anemia. These two children are twenty and twenty-two years of age respectively. They live at home on the farm and appear to be very healthy. The son showed: Hemoglobin, 75 per cent; red cells, 4,020,000; white cells, 8000, with free hydrochloric acid in the stomach contents. The girl had: Hemoglobin, 68 per cent; red cells, 4,230,000; white cells, 7200. She also had free hydrochloric acid in the stomach. Their blood smears were normal. The fact that they live the healthy outdoor life of farmers makes the count of some significance, at least it does not suggest the anemia that one often sees from indoor life.

The fifth generation includes four children, three girls and one boy between the ages of eight and fourteen. They were taken more for future record than for any data they might now disclose. No gastric examinations were made on the children and the counts were normal. They appear on the chart reading from left to right as follows: Hemoglobin, 80 per cent; red cells, 4,200,000; white cells, 8200. Hemoglobin, 80 per cent; red cells, 4,420,000; white cells, 8200. Hemoglobin, 70 per cent; red cells, 4,450,000; white cells, 5800. Hemoglobin, 84 per cent; red cells, 4,440,000; white cells, 6000. The blood smears in all were considered to be normal.

The hemoglobin estimations throughout were made by the same Dare apparatus and we have been accustomed to consider a reading of 90 per cent with this apparatus as being our normal upper limit.

Summary. A summary of our findings would be as follows: The fifth generation are children and are included more for future record as we would not expect any evidence of anemia to develop at this age of life. In the four generations, there is undoubted evidence that a severe form of anemia, which has usually produced death, has been present. In the first and second generations, the evidence is based on the history of the cases and with the exception of the first generation on the observation of the family physician and one of the older members of the family. For many years it has been known among the physicians of the community that this anemia was present in this family. In the third and fourth generations, where most of the cases occur, the observations from the medical point of view are more accurate and trustworthy. In all there have been 17 cases of anemia, 13 are dead and 4 are living. Of the 13 that are dead the family physician vouches for 7 as being due to pernicious anemia. The one who died at the Warren State Hospital was diagnosed pernicious anemia and as this is one of the very efficient institutions in this community, we do not see how we can do other than accept this diagnosis. We, ourselves, have undoubted proof that one died of pernicious anemia. The 4 cases in the first and second generations are the only ones where accurate proof obviously is wanting, but we have every reason to believe that they had this family anemia and died of it. The three members in the second generation were all well known in life by members of the family who are still living. The original ancestor is the only one whom no one living has ever seen but we have been assured that the history that he had an anemia and died from it, is correct. Of the 4 cases living, we have seen 3 and they are undoubted cases of pernicious anemia. The other living case has been diagnosed pernicious anemia by a competent observer in one of the Pittsburgh hospitals. It would appear, therefore, that there is reason to believe that the type of anemia which runs through this family has been of a very severe grade and in all probability of the socalled pernicious or primary form. It is further interesting that there are seven instances of secondary anemia as indicated by the blood count in the third and fourth generations. In one of these cases there is a very low free hydrochloric-acid content in the stomach and in the blood smear some tendency to the formation of the large red cells. We hope to be able to watch this case over a period of years because there are suggestive signs in the blood without the absence of free hydrochloric acid in the stomach.

It is our hope to add the data obtained from additional members of this group so that eventually we may be able to have a fairly complete outline of this rather unusual family.

BIBLIOGRAPHY.

1. Bartlett: J. Am. Med. Assn., 1913, **60**, 176.
2. Bramwell, B.: Anemia and Some of the Diseases of the Blood-forming Organs and Ductless Glands, 1899, p. 76.
3. Cabot: Osler and McCrae: A System of Medicine, 1908.
4. Gilbert and Weil: Bull. et mém. hôp. de Paris, 1910, **30**, 543.
5. Gilford: Lancet, 1923, **1**, 64.
6. Gram: Ugeskr. f. Laeger, 1921, **83**, 636.
7. Gulland and Goodall: The Blood, 1912, p. 126.
8. Klein: Quoted by Schauman.
9. Levine and Ladd: Bull. Johns Hopkins Hosp., 1921, **32**, 254.
10. Matthes: Verhandl. Deutsch. Kong. f. inn. Med., 1913, **30**, 290.
11. Minot: Oxford Medicine, **2**, 612.
12. Meulengracht: Ugeskr. f. Laeger, 1920, **82**, 777; Am. J. Med. Sci., 1925, **169**, 177.
13. Mustelin: Acta. med. Scand., 1922, **56**, 411.
14. Patek: J. Am. Med. Assn., 1911, **56**, 1315.
15. Roth: Ztschr. f. klin. Med., 1914, **79**, 266.
16. Schauman: Finska lakaresallskapets handlingar, 1911, **53**, 133.
17. von Decostello: Wien. klin. Wchnschr., 1923, **36**, 258.
18. Willson: J. Am. Med. Assn., 1912, **59**, 767.

PERIODIC VARIABILITY OF SOME FORMS OF ARTERIAL HYPERTENSION.

By Louis H. Sigler, M.D.,

Brooklyn, N. Y.

Much has been written on the diurnal changes in blood pressure readings in the normal as well as in the hypertensive blood-pressure cases. Posture, activity, digestive processes and nervous excitement are given sufficient recognition as determining factors in increasing or decreasing the pressure readings of a given individual at any given time. Such variability, however, lasts only so long as the cause bringing it about is operative. Change that cause and the reading changes almost immediately.

No emphasis has, however, been laid on the hypertensive cases showing periodic variabilities bordering on the normal or even subnormal only to return again to the original reading. In these cases, such changes occur without any evident or recognizable causes, last for periods of hours or days and are apparently unassociated with any other physical or mental disturbances than those experienced by the individual during the hypertensive period.

To my mind, its appreciation is of great value for various reasons: (1) It confirms the present accepted belief that hypertension is not the result of anatomic pathology of the cardiovascular system such as angiosclerosis or cardiac hypertrophy; (2) it may throw some light on the causation of hypertension; (3) its recognition will sometimes prevent unjust criticism of a physician who impressed

a given patient with the existence in his or her case of high blood pressure, when it might not have been found on a different day by another physician; (4) and to the interest of the medical examiner for insurance companies, a normal blood pressure reading in some cases at the time of examination has, of course, no significance in ruling out hypertension. This is particularly important in cases where no appreciable pathologic changes in the bloodvessels or in the size of the heart are found.

The recognition of this factor is also of importance in discrediting many of the prevailing "cures" for hypertension. There is a tendency from time to time to attribute a fall in blood pressure to one or another method of treatment, proclaiming that method a cure. If the class of cases under consideration is a criterion for the value of such cures, we certainly must admit that so far nothing specific in the form of treatment exists. We find here the fall of pressure to occur without treatment as well as with treatment and to rise again in spite of treatment. When the fall occurs we may feel triumphant over a discovery of a cure, not stopping to inquire if the fall might not have occurred also without any treatment whatever.

Illustrative Cases. CASE I.—J. F., female, aged fifty-three years, had rheumatic fever at twenty-two years of age, disabling her for two months. Since then she has had occasional vague aches and pains in various muscles and joints but felt well generally.

I first saw her in January, 1923, at which time her only complaint was pain between some of the toes of her left foot which I found to be due to small callosities, and which was relieved on their removal. On physical examination, I found her to be rather healthy looking, well developed, of good color, gums somewhat pyorrhetic, throat chronically inflamed. The heart was slightly enlarged with a systolic murmur at the second right interspace, 3 cm. from the midsternal line, not transmitted. Her blood pressure in the sitting position was systolic, 210; diastolic, 110.

I did not see her again until October, 1923, at which time she complained of general weakness and nervousness. The reason she gave me for not seeing me before was that another physician told her three months after I saw her that her blood pressure was perfectly normal and that my determination was not correct. About four months later, she was rejected by an insurance examiner because of hypertension and she, therefore, came back to me. At this time I found her pressure to be systolic, 145; diastolic, 90. This remained approximately the same for three days after which time I did not see her again until July, 1925. At this time she complained of marked palpitation on exertion and great weakness. Her blood pressure now was systolic, 210; diastolic, 120. I put her on potassium iodide and bromides, ordered a salt-free diet and as much rest as I could impose upon her and cut down her food intake especially

that of nitrogenous material. I saw her again in September, 1925, at which time with all this treatment her blood pressure was systolic, 190 to 220; diastolic, 110 to 120. After one week rest in bed her pressure was systolic, 165; diastolic, 100.

CASE II.—S. P., female, aged fifty-five years, was first seen in March, 1923, when she complained of precordial oppression, headache, dizziness and symptoms of gall bladder pathology. The heart sounds were accentuated, the blood pressure, systolic, 160; diastolic, 80. I saw her again in November, 1923 at which time her blood pressure was systolic, 130; diastolic, 75. In December, 1924, she complained of great weakness on exertion. Her blood pressure at this time was systolic, 120; diastolic, 80. She showed now moderate thickening of her radials and slight arcus senilis. No treatment was given at any time with a view of lowering the blood pressure.

CASE III.—A. F., aged sixty years, female, came to me in October, 1923, with complaints of shortness of breath on the slightest exertion, with sensation of fainting on and off for the past few years, lasting a variable period of days. Examination showed auricular fibrillation. There was a total irregularity of heart, rate of apex, 150; of pulse, 110. There were marked signs of decompensation. Her blood pressure at this time was systolic, 110 to 160; diastolic, 70. That is, at 110 all the palpable pulses were heard while at 160 only about one out of every five was heard. I ordered her to bed and put her under complete digitalis control in two days. At this time her heart was regular, rate 71, and pressure systolic, 145; diastolic, 90. I saw her again in March, 1925, at which time she complained of some shortness of breath, loss of appetite, weakness and occasional palpitation. The heart was regular, rate 72; pressure: systolic, 200; diastolic, 120. The urine showed considerable albumin, with several granular and hyaline casts. I did not see her again till December, 1925. At this time, she told me that she felt rather comfortable since I saw her last. Her pressure now was systolic, 150; diastolic, 100; the heart was regular. She felt weak and dyspneic at times. Her urinary findings were the same as before.

CASE IV.—E. F., female, aged thirty-seven years, was first seen in June, 1924, with complaints of dizziness on and off for the past five years coming on at infrequent intervals, each attack lasting one or more hours and associated at times with vomiting. At times she experienced also some ringing in the right ear. The heart was not enlarged. There was a systolic murmur heard between the third left and second right costosternal junctions. Her blood pressure was systolic, 170; diastolic, 80; pulse rate, 100 to 110. I put her on bromides. Nine days later her pressure was systolic, 138; diastolic, 80; with all symptoms, except tinnitus, gone. I saw

her again in January, 1925, at thich time her blood pressure was systolic, 150; diastolic, 90.

CASE V.—G. T., aged fifty-eight years, female, came to me with a chronic eczema involving the anterior portion of the right leg. She had had that condition several years, clearing up somewhat at times but reappearing again in its full flourish at other times. Physically there was nothing abnormal to be found except for a marked pyorrhea. Urine and blood chemistry were normal and the Wassermann negative. Her pressure was systolic, 174; diastolic, 88. I saw her again one month later during which time she received no other treatment than local applications to the eczematous patch. Her pressure now was systolic, 140; diastolic, 88.

Comment. The cases here cited were selected from a series of over 150 hypertensive cases seen in private practice. I have encountered similar cases in my clinic work at the Greenpoint and New York Post Graduate Hospitals, and have no doubt that everyone taking blood pressures has met with such instances, although I have found no reference in literature of such marked fluctuations. In every instance the pressure readings were taken under as nearly equal conditions as possible, eliminating the effects of excitement, change in posture, and so forth.

Although comparatively rare, its occurrence in the presence and absence of definite cardiovascular pathology makes one feel that hypertension is not dependent upon an anatomically abnormal heart or bloodvessels but is rather the cause of it. Thus, Case I presented a hypertension with practically no cardiac enlargement when first seen, a normal pressure later, and marked cardiac enlargement still later as a result of the persistent hypertension. Case II, without arteriosclerotic changes detectable at first, presented such changes later, and these concomitant with a lower pressure. In Case III, we may ascribe the abnormal pressure to abnormal cardiac action during fibrillation and the subsequent normal pressure to the return of the heart to a normal rhythm, but we cannot explain the rise in pressure later. Should we attribute such rise to the coexisting nephritis, why did it fall again still later in spite of the persistence of this condition?

In trying to solve the riddle of hypertension, attempts have also been made to attribute the phenomenon to certain end products of nitrogen metabolism, to internal secretions and to dietary errors. Applying these hypotheses to the variations under consideration, we may argue that with the accumulation of these products in the system there is a hypertensive period and with their elimination, detoxication or fatiguing effects upon the circulation, the blood pressure falls. No definite proof of such factors as being the causes of hypertension has been brought forward, however. High protein

diet, long blamed for hypertension has been shown by Strouse and Kelman[1] to be without effect on pressure in hypertension. Disturbances of sodium chloride metabolism as a cause has been disproved by O'Hare and Walker[2] and by Mosenthal and Short.[3] Increased adrenalemia as a factor has no scientific support. It has never been proved by blood analysis, and according to Schmorl[4] the adrenalin content in the suprarenals is the same in normals in hypertensive cases. Oppenheimer and Fishberg[5] cite 9 cases from the literature and 2 cases of their own where hypertension was supposed to be caused by suprarenal cortical tumors. The fact that many such cases, according to the same authors, are not associated with hypertension, would seem to point to the mere coexistence of the two conditions rather than to their interdependence.

In the illustrative cases cited in this paper, there were no changes in the modes of life or in the dietaries of the patients that could be held responsible for the variations in the pressure readings at the different periods. Both during the high- and low-pressure periods, the diets, the home environments, the work or rest and all other factors that may influence the blood pressure were identical, yet this marked variation.

It would seem as if changes of this kind are dependent mainly upon instability of the vegetative nervous system. Having eliminated as far as possible the other factors that may account for them, this conclusion seems logical. The condition may be analogous to instability of the psyche in insanity cases with periods of exacerbations and remissions, independent of the general constitutional state. This assumption would explain the occurrence of the phenomenon under various constitutional states, and would obviate the necessity of classifying and subclassifying hypertension into various groups to conform with some hypothetical causes and occasional coexisting body condition. It would explain the occurrence of the condition with or without nephritis, arteriosclerosis, diabetes, suprarenal tumors and the like, and would also explain the existence of these diseased states with or without hypertension. It would simply mean that an individual to have hypertension must have some peculiarity in his vegetative nervous system exhibiting itself in the form of marked or moderate pressor vasomotor phenomena. In other words, for hypertension to occur, there need not necessarily be a diseased condition of any other system but there must be some structural or functional abnormality in the vegetative nervous system making it susceptible to stimuli—toxic, infectious, neurogenic or metabolic—that under ordinary circumstances are ineffective. I venture to suggest even structural disturbance because, to my knowledge, no attention has been paid in the past to determine the possible anatomic alteration of the vegetative system in the hypertensive. All researches—laboratory or postmortem—have been directed toward other systems in an attempt to explain this phenomenon.

Clinically, there is some proof to be found for this hypothesis. There are always some other manifestations of vegetative disturbance to be found in these individuals, that have of late years come to be looked at as autonomic imbalance. Kessel and Hyman[6] described a definite syndrome of this class of patients proving its independence of adrenalin secretion. The manifestations vary in form with the part of the vegetative system affected, but all are part and parcel of disease of the same system.

Summary. Five cases are shown with periodic variations in blood-pressure readings ranging from marked hypertension to subnormal. The pathologic changes in the circulatory and renal structures, as shown by clinical manifestations, could not account for these variations, nor could such variations be accounted for by any change in the mode of living of the patients. It would seem that variations of this kind as well as hypertension in general are dependent upon some structural or functional abnormality in the vegetative nervous system exhibiting itself in the form of vasomotor pressor effects.

REFERENCES.

1. Strouse, S., and Kelman, S. R.: Protein Feeding and High Blood-pressure, Arch. Int. Med., 1923, **31**, 151.

2. O'Hare, J. P., and Walker, W. G.: Salt in Vascular Hypertension, Arch. Int. Med., 1923, **32**, 283.

3. Mosenthal, H. O., and Short, J. J.: The Spontaneous Variability of Blood-pressure and the Effect of Diet upon High Blood-pressure with Special Reference to Sodium Chloride, Am. J. Med. Sci., 1923, **165**, 531.

4. Schmorl, quoted by Oppenheimer and Fishberg (5)

5. Oppenheimer, B. S., and Fishberg, A. M.: The Association of Hypertension with Suprarenal Tumors, Arch. Int. Med., 1924, **34**, 631.

6. Kessel, L. and Hyman, H. T.: The Clinical Manifestations of Disturbance of the Involuntary Nervous System (Autonomic Imbalance), Am. J. Med. Sci., 1923, **165**, 513.

HEMOGLOBIN ESTIMATES IN PREGNANCY.*

By William Kerwin, M.D., F.A.C.S.,

and

Lislé L. Collins, M.D.,

St. Louis, Mo.

The general appearance of a woman in the pregnant state would lead one to believe that the blood picture improves parallel with the duration of pregnancy. Nature in her effort to prepare the organism for the loss of blood that normally takes place with the loss of the ovum makes the supreme effort to bring the blood content up

* Read before a meeting of the St. Louis Medical Society, January 12, 1926.

to a high pitch; this can be verified by making hemoglobin estimates and red-cell counts at various stages of pregnancy. The proper value of blood studies is realized when we come in contact with a patient who is compelled to weather the storm of delivery at a time when normal conditions are altered and anemia in some degree exists.

In Cabot's series of 1200 cases of progressive pernicious anemia 35 began during pregnancy or shortly after parturition, 18 during the former. Commenting on this series, Osler[1] states that all can be accounted for save the severe anemias of pregnancy which have no apparent cause. The blood in the early months shows a diminution of the red cells, a low hemoglobin, a slight leukocytosis and a chloroanemia which is followed by a rise to normal at the end of the ninth month. That this type may pass into a grave and fatal form was first shown by Channing and Lebert.[2] The postpartum type, so common, begins within six weeks to two months and the anemia may progress and prove fatal in twelve weeks. There is no clue as to the nature of the hemolytic agent. The progress of the disease and blood picture suggests a hemolytic type which can be reproduced experimentally and which is caused by the poison of the Bothriocephalus. Though progressive and often pernicious in type this anemia is caused by an agent which differs in one all-important phase from that which causes the anemia of Addison, namely, when recovery takes place it is permanent and the woman may escape the disease in subsequent pregnancies. The usual blood picture in this pernicious-like type presents a high-color index, and new red cells with basophilic granules.

Larrabee[3] reports a series of 17 cases occurring in pregnancy and the puerperium, all of a severe grade. He states, that, "the blood picture may be that of secondary anemia, pernicious anemia, aplastic anemia, or it may be atypical. In this series, all severe cases with the secondary blood picture recovered. Transfusion seemed a question of expediency rather than of necessity. Eight cases presented the pernicious blood picture. Four of these recovered after transfusion while 3 of the 4 cases not transfused died. One case of the aplastic type died in spite of transfusion. A highly atypical case recovered after splenectomy; repeated transfusions having been unsuccessful."

Rowland[4] states, that, "pernicious or hemolytic anemia of pregnancy is a special form of severe anemia which occurs during the after months of pregnancy and in the puerperium. It closely resembles pernicious anemia in hematologic and clinical features, but differs radically in progress. The mortality is high in the initial attack but if the patient survives the condition does not recur. The condition is insidious in onset and apparently it is related to the physiologic anemia in the early months of pregnancy. It progresses during late pregnancy and may be of a high grade without

causing alarming symptoms. It may closely resemble the toxemia of pregnancy. Labor is usually premature and characteristically short, relatively painless, with a minimum of bleeding. Most cases are aggravated by labor and the anemia may be recognized for the first time during the puerperium. A large percentage of cases if not transfused grow progressively worse. The child is frequently stillborn. If the child lives it does not share the blood disease of the mother, although it may suffer from malnutrition."

Rowland suggest that the anemia is caused by the production of a hemolysin produced by the ectodermal cells of the chorion, and draws the following conclusions: (1) It closely resembles pernicious anemia, but if the initial attack is overcome it does not recur. (2) The anemia comes on insidiously and may become apparent during late pregnancy or puerperium. (3) Premature labor is short, painless, and with little bleeding. Still births are frequent. (4) All toxic pregnant patients should be examined for anemia. (5) Early diagnosis is important.

Thompson[5] draws the following conclusions from a study of twelve cases: the red cell count is high at the extremes of pregnancy and low during the intermediate months. The hemoglobin is low until the seventh month, rising gradually to the ninth, that is, ranging from 67.5 per cent the second month, 65 per cent the fourth and gradually rising to 85 per cent during the ninth month.

Gram[6] found an average of 84 per cent hemoglobin in 40 non-pregnant women while the average per cent in 3 pregnant women at the fourth month was 77 per cent, in 4 at the fifth month, 67 per cent; in 9 at the sixth month, 70 per cent; in 10 at the seventh month, 78 per cent; in 32 at the eighth to tenth month, 78 to 80 per cent. In 3 cases of eclampsia at term the hemoglobin was at par.

TABLE I.—HEMOGLOBIN ESTIMATES ON PREGNANT WOMEN.

HB (per cent).	No. cases.	Av. age.	Para.						Color.		Trimester.			Wassermann.		Kahn.	
			I.	II.	III.	IV.	V.	VI.	W.	C.	1st.	2d.	3d.	+	−	+	−
55	2	36	..	..	..	..	..	2	1	1	..	1	1	..	2	..	2
60	5	23	1	..	3	..	..	1	2	3	1	2	2	..	5	1	4
65	3	20	1	1	..	1	..	..	3	...	1	1	1	..	3	..	3
70	19	23	4	5	2	2	2	3	6	13	2	8	9	6	13	4	13
75	11	28	2	2	1	..	..	6	3	8	1	4	6	2	9	9	8
80	55	24	11	11	12	7	6	6	23	32	9	18	28	9	46	8	38
85	44	25	7	15	8	6	2	8	14	30	6	24	14	12	32	6	26
90	49	24	11	7	9	9	1	10	25	24	6	25	18	7	42	2	29
95	11	25	7	2	2	..	1	..	6	5	3	5	3	3	8	..	9
100	5	22	3	..	..	..	1	1	1	4	1	.	4	2	3	1	3
Total	204		47	43	37	25	13	37	84	120	30	88	86	41	163	31	135

Schmidt[7] states, "there is little evidence in the literature to support the statement that the disease usually begins during preg-

nancy. On the contrary it is most frequently observed following delivery. The severity of the anemia, the high-color index, the leukopenia, and the presence of nucleated cells especially megaloblasts, have been responsible for confusing the disease with pernicious anemia. That megaloblasts occur in many forms of anemia is well known. Pernicious anemia is a severe form which after one or more remissions ends fatally, and develops as a primary disease without a demonstrable cause. Puerperal anemia should not be confused with primary pernicious anemia which produces a somewhat similar blood picture. The absence of macrocytes and the frequent leukocytosis may serve to differentiate it. Other differences are the lack of remissions and especially the absence of cord lesions."

TABLE II.—HEMOGLOBIN ESTIMATES ON PREGNANT WOMEN WITH NEGATIVE WASSERMANN REACTIONS.

Trimester.	Number cases.	Hemoglobin estimates (per cent).		
		Lowest.	Highest.	Average.
First	30	60	100	89.1
Second	88	55	95	83.2
Third	86	55	100	83.0

TABLE III.—HEMOGLOBIN ESTIMATES ON PREGNANT WOMEN WITH POSITIVE WASSERMANN REACTIONS.

Trimester.	Number of cases.	Hemoglobin estimates (per cent).		
		Lowest.	Highest.	Average.
First	10	75	95	82.8
Second	14	70	95	83.4
Third	14	70	100	86.1

From a study of the cases so far reported one would be inclined to the opinion that infection is the most probable cause of puerperal anemia. Grawitz, Sachs, and others support the toxic theory. The doctrine of a toxin produced within the ovum and causing anemia in the mother is not well supported by facts. It has been demonstrated that removal of the uterine contents does not relieve the condition; in fact induced abortion has a decidedly unfavorable effect. Furthermore, the anemia is most frequently seen following delivery.

Galluope and O'Hara[8] in summing up puerperal anemia believe it to be an entity in itself.

During the past three years, we have been making hemoglobin estimates of cases attending the Cass Avenue Prenatal Clinic and have found values ranging from 55 to 100 per cent. In 30 cases during the first trimester, the average hemoglobin was 83.1 per cent, the lowest being 60 per cent and the highest 100 per cent. In 88 cases during the second trimester, the average was 83.2 per cent, the lowest being 55 per cent and the highest 95 per cent. In 86

cases during the third trimester, the average was 82 per cent, the lowest 55 per cent and the highest 100 per cent. The series includes cases with positive Wassermann reactions, some remaining untreated. The patients (most of whom belong to the working class) are of all nationalities, and range in parity from 1 to 10 +. The ages range from fifteen to forty years. The average estimate in forty-seven primipara was 84 per cent, the lowest 80 per cent, and the highest 100 per cent; in thirty-seven third para the average was 82 per cent, the lowest 60 per cent and the highest 95 per cent; in twenty-five fourth para, the average was 83 per cent, the lowest 65 per cent and the highest 90 per cent; in thirteen fifth para, the average was 82 per cent the lowest 70 per cent and the highest 100 per cent; in thirty-seven sixth para and plus, the average was 80 per cent, the lowest 55 per cent and the highest 100 per cent.

Most of the cases were in the early twenties and, therefore, in a good state of health and not burdened with the responsibilities of large families. In women under twenty years of age the hemoglobin average was 83.1 per cent, between twenty and twenty-five the hemoglobin average was 82.5 per cent, between twenty-five and thirty the hemoglobin average was 81.3 per cent and over thirty the hemoglobin average was 83.7 per cent. Ten cases in the first trimester of pregnancy with a positive Wassermann reaction, showed an average hemoglobin of 82.8 per cent, the lowest 75 per cent and the highest 95 per cent; 14 cases in the second trimester with a positive Wassermann reaction showed an average hemoglobin of 83.4 per cent, the lowest was 70 per cent and the highest 95 per cent; 14 cases in the third trimester with a positive Wassermann reaction showed an average hemoglobin of 86.1 per cent, the lowest was 70 per cent and the highest 100 per cent. In all there were 38 patients with a positive Wassermann reaction and these showed an average hemoglobin estimate of 84.1 per cent.

Of 166 patients with a negative Wassermann reaction, 22 in the first trimester showed an average hemoglobin of 82.5 per cent, the lowest was 65 per cent and the highest 90 per cent; 65 in the second trimester showed an average hemoglobin of 82.5 per cent, the lowest was 55 per cent and the highest 100 per cent; 78 in the third trimester showed an average hemoglobin of 81.4 per cent the lowest was 60 per cent and the highest 100 per cent.

Syphilis is frequently a factor in severe cachexia, but in this relatively small series of cases it did not play a role, for the positive Wassermann cases showed a higher hemoglobin percentage than those with a negative Wassermann.

All cases showing a low hemoglobin estimate were put on treatment, including arsenic, iron, diet, and hygienic measures, with the hope of bringing the hemoglobin up to par at the earliest possible date. Needless to say, it is of the greatest importance to observe closely the patients who show a marked anemia, not alone because of

the present and future health of the mother, but also because of the child's welfare. Whether or not the anemic mother is capable of nourishing her offspring is a question we hope to solve in work that is being done at the present time through coöperation with our child welfare center. These results we hope to publish in the near future.

Conclusions. 1. Because of the frequency with which severe anemia occurs in pregnancy and the puerperium it is important to make hemoglobin estimates during the different stages of pregnancy.

2. Old multipara are more prone to develop anemia than are primipara or multipara at an earlier age.

3. In late pregnancy, anemia is more apt to occur than in early pregnancy.

4. Syphilis has no bearing on the anemias of pregnancy.

5. Patients with a low hemoglobin should be vigorously treated.

REFERENCES.

1. Osler: Brit. Med. J., 1919, **1**, 1.
2. Channing: New England Quart. J. Med. and Surg., 1842, **1**, 157.
3. Larrabee: Am. J. Med. Sci., 1924, **168**, 47.
4. Rowland: J. Am. Med. Assn., 1924, **82**, 372.
5. Thompson: Johns Hopkins Hosp. Bull., 1904, **15**, 205.
6. Gram: Abstract, J. Am. Med. Assn., 1921, **76**, 692.
7. Schmidt: Surg., Gynec. and Obst., 1918, **27**, 596; J. Michigan Med. Soc., 1921, **20**, 92.
8. Galloupe and O'Hara: Boston Med. and Surg. J., 1924, **190**, 161.

VARICOSE ULCER: MECHANISM OF ITS CAUSATION AND CURE, WITH NOTES ON THE ASSOCIATED PAIN AND PUPIL INEQUALITY.

By Joseph Byrne, A.M., M.D., LL.D.,
NEW YORK.

For some decades passed various methods have been employed in the treatment of varicose ulcer. When I was a junior intern, the method in my hospital consisted of spreading a stimulating or soothing ointment upon the ulcer which was then covered with a gauze pad held in place by a casually applied bandage. The house surgeon who did the dressings was a marvel of speed and the 20 or 30 patients were disposed of, as far as the daily dressing was concerned, in as many minutes to the admiration of the assisting nurses. When I became "house," the dressings consumed all the forenoon and often a goodly portion of the afternoon. Complaints were made of my slowness and I barely missed serious trouble with the

visiting staff. As time progressed, however, the "discharged cureds" exceeded the "admissions" for this particular malady and now the more chronic cases, some of whom had been in the hospital for over seven years, received more attention with the result that they too began an exodus which ended only when the last "boarder" went out to hunt a job. In private practice the treatment for the most part was as outlined above; the practitioner at the beginning of treatment forestalling failure or protracted healing by hinting that it might not be good for the patient's general health to have the leg heal too quickly. This was the good psychotherapy from the physician's, if not from the patient's, standpoint.

The various methods of treating varicose ulcer may be tabulated according to the principal therapeutic factor in each, the leg in all cases being kept as clean as possible: *Non- and Semi-surgical Methods.* (*a*) Recumbency and elevation. (*b*) Support for the veins by bandages, rubber (Martin) or other, or by elastic stockings, and so forth. (*c*) Compression bandage over cotton (Guérin). (*d*) Strapping with adhesive strips (Boynton). (*e*) Rubber tissue or other protective. (*f*) Powders of various kinds. (*g*) Powders, for example, boric acid with several layers of rubber tissue superposed and held in place by adhesive strips (Scott-Schley). (*h*) Warm fomentations, for example, of boric acid, acetate of aluminum, lead acetate, and so forth, especially in beginning treatment of neglected cases with much swelling, and so forth. (*i*) Cauterization with phenol, stick $AgNO_3$ or actual cautery. (*j*) Support for veins by alternate layers of warmed (liquefied) Unna's paste and gauze bandaging. (*k*) The "moist chamber" made by encircling the ulcer with a low, stout wall of ZnO ointment the ulcer surface being covered by a protective of rubber tissue strips, and so forth, over which is placed an absorbent dressing and a bandage (Schweig). (*l*) Exposure to Roentgen ray, radium, sunlight and air, and so forth. (*m*) Injection of cicatrizing substances into walls of the varicosed veins (Sicard) or of the femoral vein, or into the tissue surrounding the ulcer. (*n*) Scrubbing the ulcer with nailbrush and soap and water, and so forth.

Surgical Methods. (*a*) Excision of the varicosed veins. (*b*) Multiple ligation of the veins. (*c*) Ligation of the femoral or internal saphenous vein. (*d*) Circumcision of skin of leg above ulcer, or of ulcer itself the skin being sutured after ligation of veins. (*e*) Skin grafting (Thiersch method). (*f*) Grafting of entire thickness of skin nonpedunculated (Krause) or pedunculated. (*g*) Small clippings of epidermis strewed over the granulating surface (Reverdin). (*h*) Stretching of nerves supplying skin area in which ulcer is situated (Bardescu and Chipault). (*i*) Curettage. (*j*) Incision of cicatrized ulcer margin with or without circumcision of the ulcer (Nussbaum).

Pathology. In the mechanism of necrosis in any location, circulatory stasis is a feature and in varicose ulcer it is the fundamental

factor. The stasis primarily is the result of failing local circulation which in turn rests upon interference with or failure of the mechanisms which maintain the local bloodflow. These are: (1) The heart and auxiliary mechanisms (external respiratory mechanism, skeletal musculature) which help it to drive the blood and lymph toward the right heart along the valved, one-way venous and lymphatic channels; (2) the vasomotor nerves and the vascular musculature supplied by them more especially that of the arterioles and veins (venomotor system). The capillaries have vasomotor innervation[1] and both capillaries and venules are capable of contracting actively as Hooker[2] has shown. Normally the circulatory mechanisms are just barely able to secure the return flow from the feet with the patient in the erect posture or sitting with the legs pendent. The blood-pressure gradient is such as to permit the flow from the arteries with a maximum pressure ranging from 120 to 150 mm. Hg in the aorta through the capillaries at a pressure of of about 37 mm. Hg (in the hand) to the veins where the pressure normally averages from about 14 mm. Hg in the crural vein to a few millimeters above or even below zero in the great veins low in the neck. Thus the venous pressure barely suffices to secure, with the aid of muscular contraction in coöperation with the vein valves, the return flow to the heart. Anything, therefore, which obstructs the flow through the larger veins (for example, the iliac, femoral, internal saphenous) has a tendency to raise the intravenous pressure in the lower portion of the leg thus retarding or completely obstructing the peripheral circulation and favoring the development of varicose veins. Hence one finds tabulated as *causes* of varicose veins pendency of the limbs, too much walking or standing, sitting, especially with knees crossed, pregnancy, constipation, pelvic tumors, tight encircling garters, defective innervation, femoral phlebitis, etc. In sedentary, and other more or less static occupations in which the auxilliary mechanisms are not brought into play the return flow from the legs steadily declines. With this the metabolic exchange in the musculature of the limb and more especially in the walls of the cutaneous arterioles, capillaries, venules and veins deteriorates progressively. As a consequence of their lack of tonus the skin veins become dilated and retain a considerable amount of more or less stagnant blood. The dilatation of the veins renders their valves incompetent and this furthers the progress of the mischief, as the long columns of blood now add their "head pressure" to the normal intravenous pressure (14 mm. Hg), thus tending to overbalance, or actually overbalancing, the intracapillary pressure (37 mm. Hg) so that the local capillary bloodflow in the skin becomes obstructed or diverted and in places even reversed. The net result in the case of varicosed veins is impairment of local blood and lymph flow, failure of metabolic interchange and *increased tissue vulnerability*. The deviation of the bloodflow to the deep veins does not compensate the circulatory

defect caused immediately by the increased pressure in the dilated veins with incompetent valves. A secondary mechanistic factor in varicose ulcer is infection which in turn impairs the bodily efficiency, general and local, and markedly disturbs endocrine function, more especially the adrenals. All these in turn impair the efficiency of the circulatory mechanisms and thus tend to aggravate or perpetuate the local disorder. As *complications* of varicose ulcer one may encounter erysipelas, lymphangitis, venous thrombosis usually accompanying phlebitis, embolism, pyemia. In very severe cases adjacent tissues or even joints may become involved with resulting bone or soft tissue necrosis, ankylosis, contractures and deformities.

In healing, the fundamental factor is restoration of the local circulation. This is essential for healthy granulation and permanent epidermization. Usually epidermization proceeds from the ulcer margin but it also spreads at times from islets of skin which occasionally persist within the ulcerated area. Cicatricial formation at the ulcer margin is a secondary factor in the local circulatory impairment that tends to perpetuate varicose ulcer. In the strangulating process that takes place at the cicatrized margin the nerve fibers are also involved. This and the neurotoxic effects from absorption are the fundamental factors in the mechanism of the pupil inequality as well as of the pain and tenderness so often found in varicose ulcer (Byrne[3, 4, 5]). After punctured wounds of the fingers the annoying tenderness and pain that would otherwise persist for several days disappeared within twenty-four hours after removal of the tiny indurated cicatrix. Finally every ulcer found in association with varicose veins is not fundamentally of varicose origin. The impaired circulation and the varices may be factors but productive lesions such as gumma, etc., or metabolic disorders such as diabetes, Ca deficiency, and so forth, may at times be the fundamental factor which calls for recognition and treatment.

Treatment. This must be directed to the fundamental factor, that is, the impaired local circulation. This is an essential prerequisite for cure and prevention of recurrence. Many cases of moderate severity are cured by measures that relieve the local circulation. In the more severe cases measures intended to relieve the local circulation, such as bandaging and so forth, may prove embarrassing in other directions, for instance, by obstructing drainage, or causing ischemic necrosis of the granulating surface or even of nonulcerated areas. Here treatment resolves itself into technical procedures to meet such difficulties. The course I have followed with success since my earliest years of practice may be outlined as follows:

1. *Cleanliness.* At the first visit, after diagnosis and evaluation of the local and general mechanistic factors (including occupation, metabolic and endocrine disorders) the patient is instructed to give the limb from knee to toes a thorough scrubbing with warm

water and soap after which a sterile gauze pad is laid over the ulcer and retained by a bandage or a clean white cotton stocking which reaches to or above the knee. The patient is further instructed to purchase in a dry goods store one roll of common cotton batting and 5 yards of unbleached muslin. The latter is to be torn into strips 3½ or 4 inches wide, which are sewed together so as to make bandages 10 yards in length. A supply of these bandages properly rolled should always be kept on hand by both physician and patient.

2. *Relief of Local Circulation.* In severe, neglected cases this is best secured by recumbency and elevation of the limb for a short time at the beginning of treatment. In addition to this if the ulcer be foul, and there is much edema, saturated solution of acetate of aluminum may be used as a wet dressing. After a few days the leg will be in such condition that a well-applied unbleached muslin bandage will so aid the local circulation that during the rest of the treatment the patient may be up and about and even working, all of which greatly helps the general health and circulation. In the less severe cases the ambulatory treatment may be begun at once.

3. *Ointments, Rubber Tissue, Drainage.* If the skin surrounding the ulcer or elsewhere be eczematous, as it often is, from discharge irritation, a thin layer of zinc oxide ointment or Lassar's paste is spread upon it taking care that no ointment is spread upon the granulating surface where its only effect would be to hamper drainage. At each dressing this ointment is removed with liquid vaseline, sweet oil or benzene. The granulating surface is now covered with slightly overlapping ½ to 1 inch strips of rubber tissue, oiled silk or even paraffin paper. A fairly thick, firm ring of common cotton batting is now made and laid over the ulcer just outside the margin so as to protect the granulating surface from undue bandage pressure. Inside this ring is placed sterilized gauze cut into small portions with a scissors. Over the gauze a small amount of sterilized absorbent cotton is placed, care being taken that the ring of nonabsorbent cotton protects the granulating surface from undue pressure. With ulcers of moderate size the cotton ring may be omitted, the granulating surface being protected by a hole about the size of the ulcer torn in the encasing sheet of nonabsorbent cotton. The hole is placed over the ulcer and within it sterile gauze is placed overlaid with absorbent cotton sufficient to fill the hole. Compression bandages are now applied. The shrinkage of the absorbent cotton by imbibition protects the granulating surface from undue pressure. Absorbent materials may be applied in different ways so long as undue pressure is avoided.

4. *Encasement in Cotton and Compression Bandages.* The leg is now encased in a layer of nonabsorbent cotton from ankle to knee. If there be ulceration about the ankle, the foot should also be included. A firm, even bandage of unbleached muslin is now applied carefully from toes to knee. A second bandage is then applied out-

side the first. This second bandage must be removed by the patient, or a member of his family, on the following morning before the patient rises from bed and another firm bandage put on. This bandage takes up the slack in the limb tissues which occurs during the night. Each morning the second bandage is replaced by a snug bandage until the patient's next visit when the whole dressing is renewed.

5. *Change of Dressings.* The dressings, as a rule, should be changed as little as possible. Saturation with exudate and the manner in which the tissues react to the soiled dressings are the governing factors. Some maceration is desirable in old ulcers as it softens the cicatrized margin and so aids the local circulation, granulation and epidermization.

6. *Strapping.* Strapping sometimes has a limited use in aiding the local circulation and macerating the cicatrized margin. It is only available for relatively small ulcers and must always be used with caution and supplemented by the bandage from toes to knee with adequate provision for drainage, and prevention of undue pressure. Strapping is contraindicated in diabetes or where there is a tendency to eczema and marked tissue vulnerability. Before strapping, the leg should be shaved. The strips should never be torn off rapidly as they may bring the epidermis off *en masse.* In ulcers occurring about the ankle, strapping supplemented by non-absorbent cotton encasement and the compression bandage has given happy results.

7. *Aids to Epidermization.* Exuberant granulations may be removed with a sharp scissors, knife or curette. As a rule they are insensitive. Novocain (5 per cent solution) may be applied on cotton (or injected hypodermically) if the ulcer be very painful or the patient very timid. The ulcer margin should be closely observed at each dressing. The delicate, liliac film indicates active epidermization but a hard, horny rim shows that active epidermization has ceased. This ring can be gently raised with a sterile toothpick or needle. Once a portion of it is raised, it can often be entirely peeled off. This should be done carefully to prevent profuse bleeding. After removal of the horny rim, active epidermization at once begins anew but the ring tends to reform and should be removed as often as it forms.

8. *Incisions of Ulcer Margin.* Sometimes in old, neglected cases light scarification or free incisions of the cicatrized margin, under 5 per cent novocain blocking, hasten the healing. The bandaging, however, tends to macerate the indurated margin, so that the strangled vessels and nerves, and so forth, are relieved.

9. *Exposure to Air and Sunlight.* These are distinct aids to hardening of the granulations, epidermization, and cornification of the new epidermal film, and should be done at every dressing for a short time. When the ulcer is "filmed over" a very thin layer of

protective ointment may be spread on its surface to replace the rubber strips. The ointment layer must be extremely thin to permit absorption of exudate with the minimum of maceration.

10. *Metabolic and Endocrine Complications.* The possibility of these must always be kept in mind and the proper corrections made as far as possible. Tight strapping and bandaging are here contraindicated, as the excessive tension may induce gangrene in diabetic patients, or blistering followed by ulceration (colliquative necrosis) in patients with calcium (parathyroid) deficiency.

11. *Endocrine Treatment.* In some cases of ulcer, endocrine disturbance is the fundamental factor, but in any type of chronic ulcer, somatic or visceral, endocrine function may be affected secondarily by enforced bodily inactivity and by the inevitable infection and toxic absorption. In all such cases parathyroid substance ($\frac{1}{20}$ gr.) and calcium lactate or chloride (gr. iii) with or without thyroid extract ($\frac{1}{12}$ to 1 gr.) may help. If the blood pressure be low (hypoadrenia) gr. i or ii of dried suprarenal body may be added to the other substances. With high blood pressure ovarian extract gr. ii to iii (even in the male), with or without pancreatic extract gr. ii to iii, may be indicated. If the basal metabolic rate be low, thyroid extract ($\frac{1}{8}$ to 1 gr.) and auxiliary thyroid preparations (pituitary extract anterior lobe (gr. ss to i), may be added, being on the watch for signs of hyperthyroidism

12. *Prophylaxis.* After healing, recurrence is prevented, just as the ulcer itself might have originally been prevented by supportive measures for the general and local circulation. In some cases surgical obliteration of the varicosed veins is indicated, as reduction of the columns of blood in the dilated veins aids the cutaneous blood and lymph flow, even though the return flow takes place as before, mainly through the deep veins. Excision or obliteration of the femoral vein is unsound in principle as it leaves the local skin circulation still hampered by the unsupported columns of venous blood and still further obstructs the flow from the superficial varicosed veins. Excision and multiple ligature of the varicosed veins as well as cicatrizing injections have more to recommend them as they remove the long columns of venous blood. But like all other surgical procedures they must be supplemented by measures to maintain or restore the local circulation (exercise, rest, bandaging). Where operative and allied procedures are not indicated, the local circulation must be maintained by bandages, or a rubber stocking. Besides these an attempt should be made, especially in the preulcerative stage, to restore or prevent further deterioration of the vasomotor tone in the lower limbs. This can be done by substituting active for sedentary occupations and by hot and cold douches, general and local. Daily exercise, mental and physical, alternated with adequate rest periods conserves vasomotor tone and is the best mobilizer and dispenser of the endocrine activators. Exercise

should be preceded and followed by rest. The optimum of rest and exercise should not be exceeded. Excess in either direction only impairs vasomotor tone. Climate and atmospheric conditions (temperature, humidity) and above all ventilation of the sleeping apartment, also influence vasomotor tone. Finally, a well-balanced diet and the avoidance of too much covering up of the limbs and body by heavy impervious clothing are important for the same reason.

Discussion. Under the treatment outlined, most ulcers of moderate size heal completely in from fourteen to twenty-one days. Extensive ulcers of years' duration also heal rapidly. In the mechanism of cure, improvement in the local skin circulation is the *sine qua non*. This is secured by general measures and by bandaging. The latter, like excision or obliteration of the varicosed veins, removes the columns of venous blood which check the blood (and lymph) flow through the skin capillaries. The ultimate escape of blood from the skin capillaries into the deep veins only partially relieves the situation. A proper bandage by compressing the veins almost to the point of obliteration supplies artificially their missing tonus leaving in them only thin columns of blood which are *now adequately supported by the vein valves* so that they no longer obstruct the capillary flow. The encasement in nonabsorbent cotton evenly distributes the compression of the inelastic bandage and affords an optimum of "give" which permits beneficial work and exercise. Absorbent cotton rapidly loses bulk from imbibition of perspiration or exudate so that the bandage compression early begins to fail. This necessitates frequent changes of dressing which retard cure. Nonabsorbent cotton moreover acts as a mild counterirritant, stimulating the nerves and smooth muscle in the skin and bloodvessels and the contractile substance in the endothelium of the capillaries and lymph spaces, thereby promoting blood and lymph flow. The ring of nonabsorbent cotton tends to macerate the cicatrized margin, thus promoting the local circulation and epidermization. As absorbent dressings directly applied adhere to the granulating surface the more superficial granulations are torn off at each dressing. The rubber strips prevent this and stimulate granulation without permitting it to become excessive. They also help to macerate the cicatrized margin.

The pupil inequality accompanying varicose ulcer has a mechanism similar to that associated with other somatic lesions. I have found experimentally[3, 4] and clinically[5] that in unilateral lesions (abscess, ulcer, adenitis, fractures) below the umbilicus, the contralateral is the smaller pupil (negative phase) so long as the animal or patient is quiescent and free from pain; but at once becomes the larger pupil (positive phase) when the animal or patient is excited or in pain. The phenomenon which I have named pseudoparadoxical[3] is observed in the homolateral eye in unilateral somatic

lesions above the umbilicus (trunk, head or neck). I have also observed the phenomenon in visceral lesions,[4] in which it is of practical importance in diagnosis and therapy. Thus lesions of the left lung (exclusive of the pulmonary artery), or of the aorta or left heart, affect the left pupil whereas lesions of the right lung or of the right heart or pulmonary artery affect the right pupil. As the lesion heals the pupil inequality becomes less and less and finally disappears although after somatic or visceral lesions a slight inequality (negative phase) frequently persists. The pupil phenomenon and the pain and tenderness in any given case are closely related, the fundamental factor in both being the same, that is, injury, mechanical or chemical, of the primary affective (pain-bearing) neurones. In visceral lesions (for example, of the heart) the existence and location of the lesion may be indicated by the pupil phenomenon taken in conjunction with the areas of referred (reflected) pain or hyperalgesia.[5] The pupil and sensory phenomena are also fair indices of the activity or quiescence of the lesion. Thus in active lesions the positive phase (relative dilatation) is commonly found in the related pupil, whilst the associated sensory phenomena are more acute. In quiescent lesions, on the other hand, the negative phase (relative constriction) is found in the related pupil the sensory phenomena being mild or absent.

Most elderly patients are affected with cardioaortic disease (myocarditis) which manifests itself in areas of deep hyperalgesia and pupil inequality. If such patients suffer from ulcer of the right leg, the pupil inequality is often very marked since the cardioaortic and leg lesions synergize in affecting the left pupil. In the Neurological Hospital on Welfare Island many leg ulcers in the aged have been observed and several of many years' standing were rapidly healed by our energetic house physician, Dr. Arnold Gottesmann, using the moist chamber or Unna's method modified. Fig. 1 shows the pupils of a patient suffering from ulcer of the right leg still in the painful stage. The most common location of the areas of deep and superficial hyperalgesia found in cardioaortic disease is set forth in the chart. Pain when present is usually referred to one or more of the deep areas on the left side within the area of superficial hyperalgesia. In a case of a large ulcer of the left leg the pupils, eye grounds and refraction, were carefully followed by me in coöperation with the visiting ophthalmologist for many years. This patient, who was of middle age, was cured by another of our capable interns, Dr. Schwartz, by the moist-chamber method. For years previous to cure, the pupil inequality was marked, the right being the affected pupil. Fig. 2 shows the pupils about equal after complete healing of the ulcer.

Study of the pupils in varicose ulcer prepares the clinician for the detection and interpretation of the changes encountered in visceral lesions.

From its prevalence and economic significance and the suffering it entails, leg ulcer does not seem to have received the attention it deserves. In one of our public institutions about 100 cases are laid

FIG. 1.—Pseudoparadoxical phenomenon (positive phase) in left pupil (larger) from ulcer of right leg in association with cardioaortitis (myocarditis).

FIG. 2.—Pupils equal after healing of large ulcer of left leg of many years' standing. Marked pupil inequality previous to healing.

up at the city's expense, and in most other cities of this country and Europe the situation is similar. This, therefore, is a problem for the administors and visiting staffs of city institutions. The

majority of these patients could, with a little attention, be so restored that they might go home and find suitable work. Leg ulcer holds scientific interest second to no other clinicopathologic condition. Some clinicians may find more interest in Roentgen ray shadows and the deductions to be made from them, but in leg ulcer Nature herself may be seen at work on the defence under adverse conditions, or busy with reconstruction under favorable, corrected conditions. Can anything have greater appeal for those interested in scientific

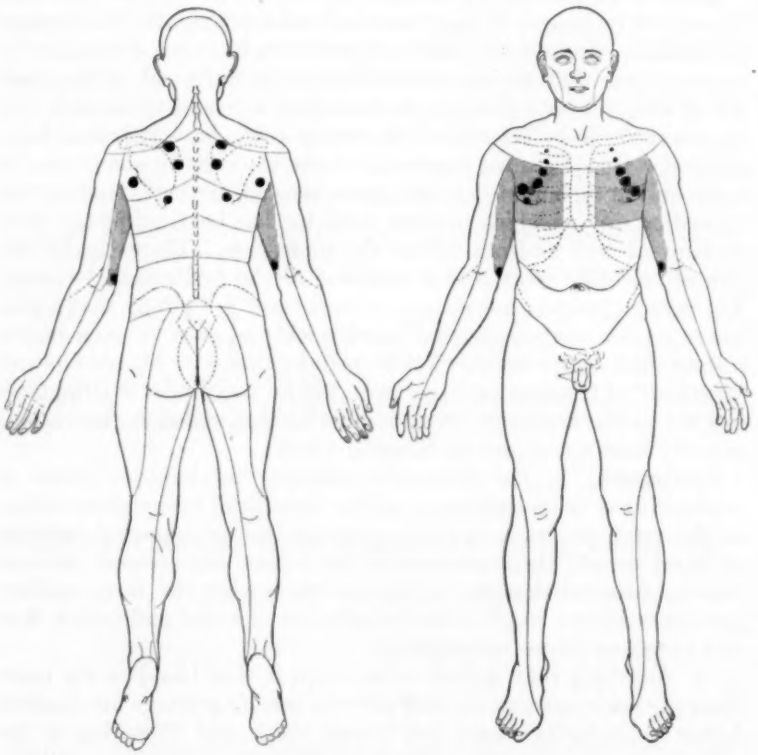


CHART.—Large, *heavy dots*, deep areas of hyperalgesia most usually found associated with cardioaortic disease; *linear shading*, superficial hyperalgesia for dragged pinpoint, usually present only after elicitation of the deep areas.

healing than direct, controlled observation of the struggle in a local arena between the mechanistic forces of life and death? This strikes home when one realizes that what one sees going on from day to day in varicose ulcer is a fair picture of what is going on unseen, and often even unsuspected, in one or other of the viscera. From the mechanistic standpoint a close analogy obtains between the retrograde and reconstructive processes in varicose ulcer and in cardiac disease. In heart lesions, as in leg ulcers, involvement of

the affective (pain-bearing) nerve fibers causes reflected pain and hyperalgesia of fairly definite distribution in addition to pupil inequality. In cardiac disease the sensory and pupil phenomena are good corroborative localizing signs and reliable indices of the activity or quiescence of the lesions. In therapy also these signs are practical adjuvants in regulating the patient's activity and rest periods. The neglected leg ulcer fairly represents what takes place in the damaged heart and the relapse that so often occurs in leg ulcer from neglect in prophylaxis has its lesson for the cardiologist.

Many of the methods of treating leg ulcer are merely modifications of surgical technique to meet some of the fundamental therapeutic indications. Indeed the numerous methods in vogue from time to time indicate that no one method has given universal satisfaction. All of which means that the fundamental mechanistic factors and the therapeutic indications resting upon them have not been fully grasped. But one must expect this to be the case for some time to come as the millenium has not quite arrived, notwithstanding the "speeding up" to which modern medicine has been subjected from without as well as from within the profession. Theoretically the aim of scientific treatment is removal of the fundamental causes. The personal factor, however, is so important in therapy that sometimes a poor method in good hands yields as good or even better results than a superior method in mediocre hands. Meanwhile any "method" of treating varicose ulcer will be welcome if it stimulates interest in the armies of prematurely disabled sufferers that crowd our city homes and chronic hospital wards.

Conclusions. 1. The immediate primary mechanistic factor in varicose ulcer is incompetency of the superficial vein valves which, in the erect or sitting posture, permits the unsupported columns of blood to add their pressure to the normal intravenous pressure thereby counterbalancing or even overbalancing the intracapillary pressure; the net result being impairment of blood and lymph flow and increased tissue vulnerability.

2. Anything that impedes the return flow of blood to the heart from the lower extremities may act as a remote primary mechanistic factor by inducing blood and lymph stasis and dilatation of the veins.

3. Secondary mechanistic factors are: infection, cicatrized ulcer margin, enforced inactivity, endocrine dysfunction and impaired metabolism—general and local.

4. The fundamental indication in surgical or nonsurgical treatment is restoration of the local circulation by removal or support of the long columns of venous blood which impede or halt the capillary flow.

5. Many surgical and semisurgical methods of treatment of varicose ulcer are unsound in principle; excision and multiple ligation are sound in principle and applicable in certain cases, but they

should always be supplemented by general and local prophylactic measures.

6. In severe, neglected cases treatment is best begun with recumbency and elevation which offset the immediate primary mechanistic factor.

7. In the majority of cases ambulatory treatment with compression bandages effects a rapid cure which may be kept permanent by prophylactic measures.

8. Study of the pain and pupil changes occurring in leg ulcer helps to a better appreciation of the sensory and pupil phenomena found in cardiac and other visceral disorders.

9. Endocrine treatment is indicated at one stage or another in almost every case of chronic ulcer, somatic or visceral.

10. Physical exercise is indicated as a cardiovascular tonic and as the best mobilizer and dispenser of the internal secretions.

BIBLIOGRAPHY.

1. Krogh, A., Harrop, G. A., and Rehberg, P. B.: Studies on the Physiology of the Capillaries, J. Physiol., 1922, **56**, 179.
2. Hooker, D. R.: The Functional Activity of the Capillaries and Venules, Am. J. Physiol., 1920–1921, **54**, 30.
3. Byrne, J.: Pseudo-paradoxical Pupil Dilatation following Lesions of the Afferent Paths, Am. J. Physiol., 1922, **61**, 93.
4. Byrne, J.: Afferent Relations of the Skin and Viscera to the Pupil Dilator Mechanism, Am. J. Physiol., 1923, **65**, 482.
5. Byrne, J.: The Pupil in Somatic and Visceral Disorders in Association with Referred Pain and Hyperalgesia, J. Nerv. and Ment. Dis., 1926, **63**, 105.

HUMAN GASTRIC RESPONSE TO MEAT AND YEAST EXTRACTS.*

By Louis M. Gompertz, M.D.,
and
William Cohen, M.D.,
New Haven, Conn.

The role of vitamins in nutrition and the consequences of deprivation of them have been so well established that, as might be expected, exploitation of such products has ensued. The prominence given to all sorts of yeast preparations only a few years ago is still very familiar. Interest has been particularly awakened in the possible physiologic action of Vitamin B, notably yeast, which is a rich source of this food factor.

Animal experimentation has shown that the use of food adequate in every respect except the requisite Vitamin B is attended with a

* Read before American Gastro-enterological Association, May 3, 1926, Atlantic City, N. J.

gradual lessening of appetite, resulting in diminished food intake and concomitantly a loss in body weight. Upon adding to such a diet some source of Vitamin B there is a return of the desire for food so that presently the normal consumption thereof is reëstablished, the vitamin-containing product apparently promoting appetite and a return to normal conditions.

Cowgill[1] and his associates have concluded that "a certain minimum amount of a given vitamin-containing preparation is necessary in order to maintain the appetite successfully over long periods of time." All investigators concede that Vitamin B is essential to normal nutrition at all ages and they particularly emphasize the important part which this vitamin plays in the life of man. Osborne and Mendel have demonstrated beyond question that Vitamin B tends to exert a most direct influence in stimulating appetite without necessarily acting directly through the digestive tract. This is not brought about by any change in the palatability of the food, for without varying the basic diet the same result is obtained by introducing the vitamin through a stomach tube, intravenously or intraperitoneally.

It is a matter of physiologic interest to observe the relationship of Vitamin B to appetite, and the subject is likewise of considerable clinical importance. Cowgill's experimental observations suggest that Vitamin B deficiency results in an alimentary disturbance and that the failing appetite may be due to such consequences as disturbances of secretion or loss of normal gastric motility. In the case of dogs having permanent gastric fistulas, he recorded the motility of the empty stomach and demonstrated that the anorexia resulting from lack of Vitamin B in the diet was associated with a diminution in the hunger contractions, until eventually the stomach became practically atonic. Improvement of the appetite or the atonic condition of the stomach could not be produced by the daily administration of beef extract which is devoid of Vitamin B, but is a potent "promotor" of gastric secretion. The administration of therapeutic quantities of material containing Vitamin B, however, caused a prompt recovery of appetite, general improvement of the animal, and presently a restoration of the former gastric contractility. Cowgill concluded, therefore, that while altered gastric motility may not be the sole cause of the anorexia, it is at least part of the syndrome characteristic of advanced Vitamin B deficiency. With respect to the possible effects on the secretory function of the stomach, the evidence is not yet very clear.

The relation of Vitamin B to secretory activity has been the subject of much controversy. Uhlman[2] (1918) working with the proprietary preparation "Orypan" concluded that Vitamin B, like pilocarpin, stimulates glands and believed that the effect could be abolished by the injection of atropin. Voegtlin and Myers[3] (1919) suggested that Vitamin B and the hormone secretin might

be identical. Lumiere[4] (1920) was of the opinion that vitamins serve as stimuli to the glands of the digestive tract. Cowgill and Mendel,[5] however, working under experimental conditions in which important technical errors of former investigators were eliminated, concluded that "there is no direct relation between Vitamin B and the secretory function of the pancreas, liver and the salivary glands." Their investigations and experiments, however, did not include gastric secretion.

At the suggestion of Prof. Lafayette B. Mendel the present study was undertaken, with a view of ascertaining the possible effects of products containing Vitamin B upon the gastric functions in man. So many food substances are reputed to effect gastric secretion that it is important to determine what common factor or factors act as secretory "promotors." Whether Vitamin B functions in this respect has not been adequately determined. Inasmuch as the vitamin has never been isolated in anything approaching a pure form, and due to the fact that it is readily available only as it accompanies natural food materials, any study of this food factor must at present necessarily be made with vitamin-containing foods or products, properly controlled with reference to the possible effect of the accompanying substances.

The present study represents an investigation of the gastric secretory response in man to simple test meals containing yeast extract, a product comparatively rich in Vitamin B. The procedure involved the use of an otherwise uniform meal, in which water, yeast extract solutions or extract of meat solutions, respectively, represented the fluid ingested. There are readily available two food products,* one prepared from yeast; the other from meat, which resemble each other closely in a variety of ways. They have a similarity of flavor and contain a number of cell constituents, such as purins and inorganic salts, in common. They differ, however, in the essential fact that one of these preparations—extract of yeast cells—the yeast extract of commerce, contains Vitamin B; the other—extract of muscle—the socalled beef extract, is entirely devoid of Vitamin B. Furthermore, the use of beef extracts as succogogues has been firmly established, thus greatly enhancing the value of this product as a control in our experiments. Accordingly a study has been made of the gastric secretory response to these two preparations.

Method of Experiment. Suitable normal subjects were selected, each one being required to take the following meals:

1. One hundred calorie portion of wheat (one shredded wheat biscuit) and 200 cc. boiled water. This served as the standard breakfast and was modified as follows:

* Substances used: Vegex, a yeast extract, corresponding to the English product, Marmite; Lemco, Liebig Co's. meat extract.

2. One shredded wheat biscuit and 200 cc. yeast solution, prepared by adding 10 gm. of Vegex to boiled water.

3. One shredded wheat biscuit and 7 gm. of Liebig's extract, and 200 cc. of boiled water.

The different amounts of beef and yeast products were selected to make both solutions as similar in flavor, appearance, and so forth, as possible. In both solutions, thus prepared, there was no free acid, but a total acidity of 34.

The following observations were made on each subject:

1. The free and total acidity of each specimen in terms of cubic centimeter of one-tenth normal sodium hydroxid.

2. Determination of gastric motility or complete emptying time. Amount of gastric secretion at the final emptying time or the end of the observation.

Samples of gastric contents were removed through a Rehfuss tube every ten minutes and the above determinations made with the various meals.

In order to eliminate or minimize the possibility that the secretory response produced by the preparations of yeast and meat solutions respectively might have been due to the acidity of these solutions themselves, the following procedure was instituted:

Two hundred cubic centimeters of water, to which acid sodium phosphate was added to produce a total acidity similar to the yeast and meat solutions, were given. The minimum increase of acidity which occurred in comparison with the effect of the standard meal of wheat cereal and water was so slight as to be practically negligible and appeared to have no bearing on the outcome.

From the results thus observed, certain outstanding features are apparent. Both extract of meat and extract of yeast, in the quantities used, promote gastric secretion.

Contrasted with the socalled standard cereal-water meal, the secretion-promoting effects are striking. The latter cannot be due, however, to Vitamin B since the results were quite as apparent in the cases where this food accessory was lacking. The problem of the nature of the stimulating factor is at once raised. The "promotor" cannot be creatin or creatinin since these are missing in the potent yeast extract. At the present time our knowledge of the chemical make-up of extracts of cells and tissues, such as muscle and yeast represent, is so utterly inadequate that the identification of the secretory factor remains to be determined. It may be noted that both types of extracts have purin derivatives and certain inorganic salts in common. It is also true that none of the test meals used were *absolutely* vitamin-free, for the cereal basis of the meal contains a small content of Vitamin B. When, if ever, Vitamin B is isolated in a state of purity, it should be possible to supplement vitamin-free test meals with the food factor for a more vigorous investigation of the problem.

The results, as reported, support the widely-held belief that the extract of meat is a "promotor" of gastric secretion and they likewise justify the addition of the palatable extract of yeast now available as an article of commerce to the limited list of gastric succogogues.

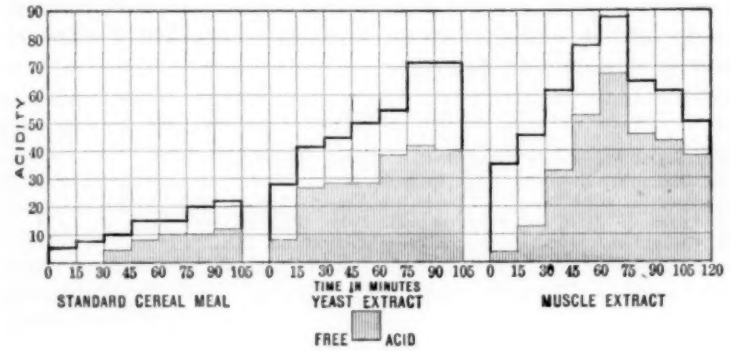


CHART I

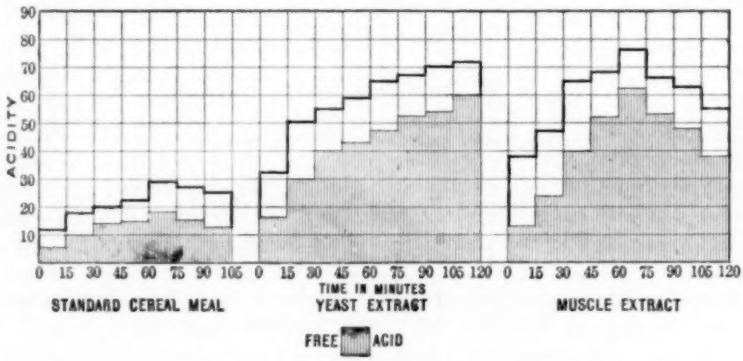


CHART II

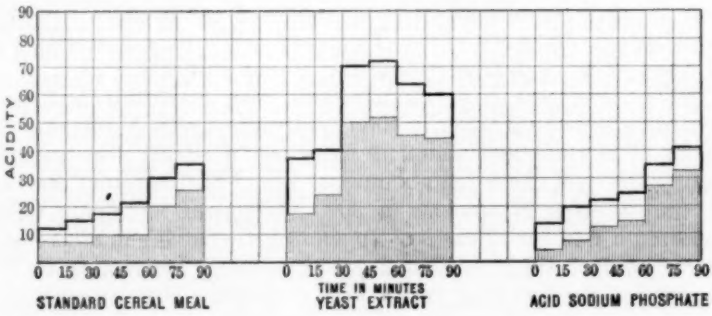


CHART III

In Vitamin B or yeast extract, we apparently have a combined tonic, succogogue and food product of undoubted clinical value. In certain pathologic conditions where meat or its extractives are prohibited, yeast products may be substituted. Such preparations may be of especial value, for instance, in hospitals where patients of certain religious beliefs refuse the taking of meat; and from this standpoint yeast-vitamin preparations may have dietotherapeutic value in appropriate conditions.

REFERENCES.

1. Cowgill, Smith and Beard, J. Biol. Chem., 1925, **63**, 11.
2. Uhlmann: Ztschr. f. Biol., 1918, **68**, 3.
3. Voegtlin and Myers: J. Pharm. and Exper. Therap., 1919, **13**, 301.
4. Lumiere: Bull. de l'Acad. de méd., Paris, 1920, **83**, 310.
5. Cowgill and Mendel: Am. J. Physiol., 1921, **58**, 131.

CHOLECYSTITIS ASSOCIATED WITH SITUS TRANSVERSUS.

Report of a Case and a Brief Review of those Found in Medical Literature.

By R. B. Bettman, M.D., F.A.C.S.,

ASSOCIATE ATTENDING SURGEON MICHAEL REESE HOSPITAL; ASSOCIATE IN SURGERY, NORTHWESTERN UNIVERSITY MEDICAL SCHOOL,

AND

Herbert F. Binswanger, M.D.,

FELLOW IN MEDICINE, MICHAEL REESE HOSPITAL.
CHICAGO, ILL.

(From the Department of Surgery and the Otto Baer Fund for Clinical Research of the Michael Reese Hospital, Chicago.)

The interest in this condition lies not so much in the fact that but few similar cases have been reported in the literature, but rather that it again emphasizes the necessity of careful and complete examinations in every case. This case, while on our wards, was of great value in demonstrating this to our students.

Situs transversus is a comparatively rare condition occurring, according to Lewald,[1] once in 5000 autopsies, once in 35,000 examinations of recruits, and about 29 times out of 40,000 Roentgen ray examinations of chest and abdomen. Bland-Sutton found one case of transposition of visceræ in 3000 abdominal sections. Willis[2] reported a number of cases of appendicitis occurring in *situs transversus* cases. What struck us as particularly interesting in this report was the fact that such a large percentage of these cases were not recognized until operation. Undoubtedly, a group of cholecys-

titis cases must have had the same history. Cholecystitis in *situs transversus* is infrequently mentioned in the literature. The cases which we find recorded are referred to below.

Case Report. M. F., aged forty-nine years, was admitted to the Michæl Reese Hospital on December 4, with a history that he had been awakened that morning with an excruciating pain in the left upper abdomen radiating along the costal margin into the left scapular region. He was nauseated and vomited once. There was a history of two previous attacks at intervals of several years. He had never been jaundiced nor had he noticed clay-colored stools. At the age of sixteen years, he had had typhoid fever. On examination, the scleræ were found to be slightly icteric. The temperature was 100.6°. The white count was 20,500. He was complaining of severe pain in the left upper abdomen and there was definite tenderness and rigidity over this area. The right part of the abdomen was neither tender nor showed any rigidity.

From the examination of the abdomen it would have been impossible to have made a definite diagnosis. The most probable diagnosis that would have suggested itself would have been an infarct of the spleen, a left paranephritic abscess or perhaps even a perforating ulcer of the cardiac end of the stomach. However, examination of the chest showed that the heart was on the right side with the apex beat definitely palpable in the right mammary line. There was no dullness under the right costal margin, in fact where the usual liver dullness should have been there was very marked tympany. Roentgen ray examination after a barium meal showed the stomach to be on the right side, the duodenum crossing over toward the left. A typical gall-bladder shadow as well as a "gall-bladder seat" or filling defect of the duodenum was furthermore seen by radiologic examination to the left of the midline.

The day following admission to the hospital the patient felt very much better and except for a slight increase in the subicteric tint of the scleræ, was apparently well. Palpation of the abdomen now definitely revealed the liver border under the left costal margin. Two days later the symptoms had completely disappeared except for a slight tenderness over the region of the left-sided gall bladder. The patient refused further treatment and went home the following day feeling entirely well. An electrocardiogram showed an inversion of all the deflections in Lead I, indicative of dextrocardia. The patient was right-handed; the right testis was lower than the left. The rectal examination was negative as far as being able to aid in the diagnosis of transposed visceræ. The patient was not a twin.

Our case is very similar to others reported in the literature. A brief résumé of several are here given:

Carl Beck:[1] A woman, aged thirty-nine years, mother of six children, complained of colicky pains in the left lumbar region. Examination showed dextrocardia and a movable left kidney. Nephropexy was performed nine days later. Recurrence of pain; left rectus resistance was found. Exploratory laparotomy showed cholecystitis with stones in a left-lying gall bladder.

Frank Billings:[2] A man, aged sixty-four years, had severe epigastric pain over the entire abdomen, but no nausea or vomiting, chill, fever and jaundice He gradually lost weight. A hard, tumor-like mass was found at the left costal margin. The stomach was distended with gas and was found to be in the right side. Diagnosis of transposed abdominal viscera made with a probable left-sided gall-bladder lesion. This was confirmed at operation and a large stone was found in the cystic duct.

H. Kehr, Hans Liebold and Neuling (in Drei Jahre Gallenstein Chirurgie), reported 310 laparotomies for gall stones with one case with a complete transposition of the viscera. *Situs transversus* was found by them twice in 10,000 autopsies.

H. Kehr reported a case, aged fifty-five years, complaining of symptoms indicative of stone in the common duct. A diagnosis of transposition of viscera was made before operation and confirmed by fluoroscope and again confirmed at operation.

Huppman:[3] A woman, mother of one child, complained of "stomach trouble and indigestion" with occasional colicky pains associated with nausea and jaundice. She passed clay-colored stools and there was tenderness over the epigastrium, radiating more to the left. The liver was palpable in the left hypochondrium; dextrocardia was found and also absence of liver dullness on the right. However, a right rectus incision was made and showed transposition of visceræ. The incision was enlarged, the gall bladder and common duct were exposed and stones were removed from the common duct.

Horn:[4] A woman, aged fifty-one years, complained of pain in the left hypochondrium with radiation to the left shoulder and marked tenderness in the left hypochondrium. Dextrocardia was noted. Roentgen ray confirmed the diagnosis of dextrocardia and *situs transversus*. Through a left-sided laparotomy a stone was found and transposition of visceræ proved.

Bell and Winn:[5] A man, aged thirty-seven years, had severe pain in the upper part of the abdomen, especially to the left, and acute tenderness in the left hypochondrium. There was liver dullness on the right side. Dextrocardia was noted on examination and confirmed by Roentgen ray, and a diagnosis of transposition of visceræ and left-sided cholecystostomy made. There was a note that this patient was right-handed and that the right testis was lower than the left.

R. E. Kelly:[6] A woman, aged forty years, not a twin, left-

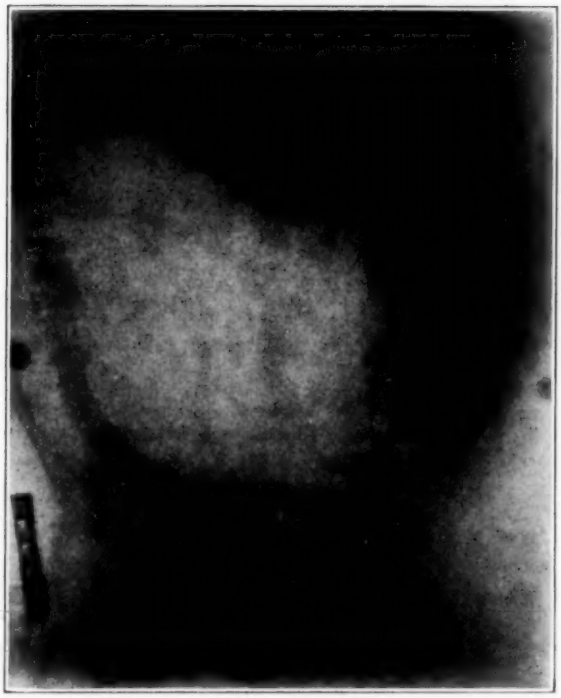


FIG. 1.—Roentgenogram after opaque enema showing transposition of the viscera: Cecum, ascending colon on the left, descending colon on the right.

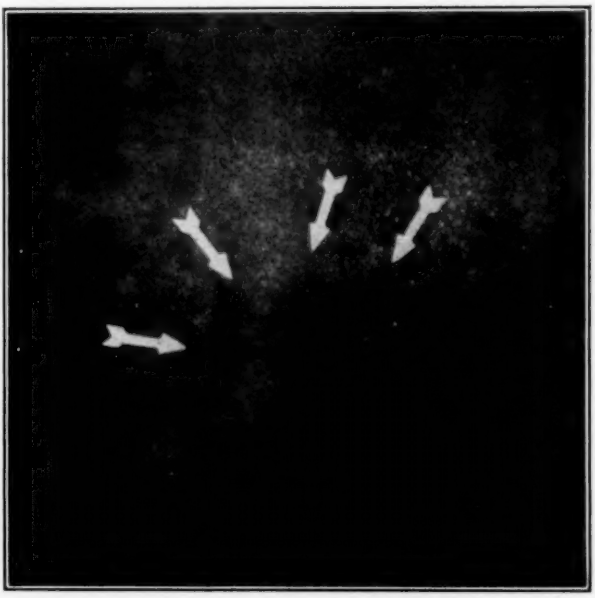


FIG. 2.—Roentgenogram showing gall bladder shadow on left.

FIG. 3.—Roentgenogram of chest showing transposed heart.

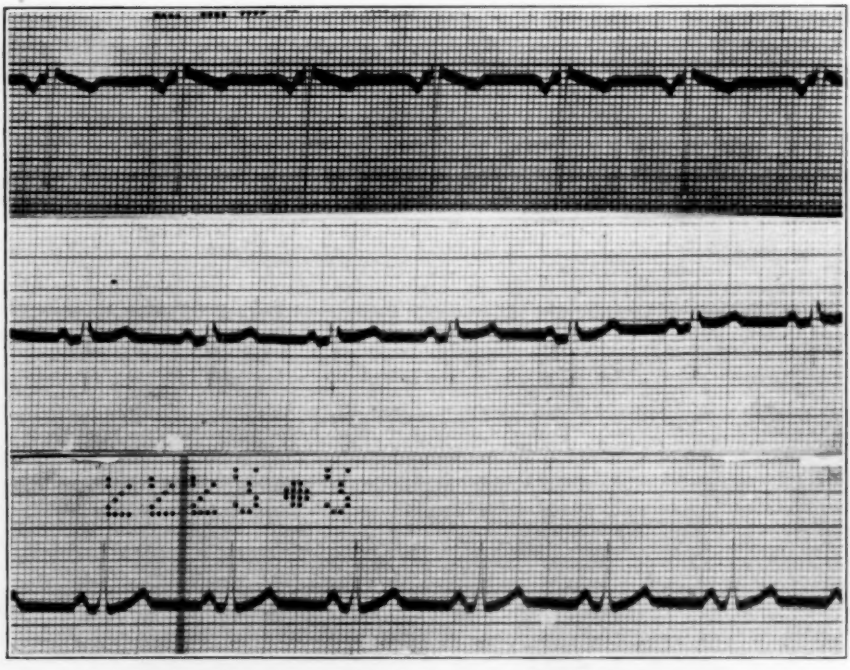


FIG. 4.—Electrocardiogram showing inversion of all deflections in lead 1.

handed, had symptoms of severe postprandial abdominal pain, situated in the right epigastrium and rising to the right scapula. The pain never rose on the left side. The diagnosis of *situs inversus* was confirmed by Roentgen ray. A lesser curvature ulcer was also demonstrated. Through a midline incision a gastroenterostomy was performed and the gall bladder full of stones was removed. *Situs transversus* was confirmed at operation.

Frishman:[7] A woman, aged twenty-three years, Para III, had pain in the left hypochondrium and under the left breast, also extending to the left back and shoulder. The patient was jaundiced and showed clay-colored stools and bile in the urine. She was right-handed. Diagnosis of dextrocardia and *situs transversus* was made. Cholecystectomy was performed and *situs transversus* confirmed at operation.

The literature on *situs transversus* is enormous. We have made an attempt only to record those cases in which gall-bladder disease was present. No satisfactory explanation for the condition has yet been offered. The condition is diagnosed as a rule by dextrocardia, the absence of liver dullness in the right hypochondrium and the presence of gastric tympany on the right side. Such items as whether or not the patient is right- or left-handed and relative position of the testicles in the male have been of no aid in confirming or disproving the diagnosis. The inversion found in the electrocardiogram is diagnostic of the condition of dextrocardia.

Summary. We have reported a case of acute cholecystitis in the presence of a *situs transversus*. Little mention of this condition has been made in the literature.

This case has been published to emphasize again the necessity of complete physical examinations in establishing diagnoses of abdominal conditions, as well as to record an unusual clinical occurrence.

REFERENCES.

1. Beck, Carl: Ann. Surg., 1899, **29**, 593.
2. Billings, F.: Phila. Med. J., 1900, **6**, 670.
3. Huppman: N. Y. Med. J., 1911, **94**, 423.
4. Horn, H. W.: Ann. Surg., 1915, **62**, 424.
5. Bell and Winn: Austral. Med. J., 1920, **1**, 339.
6. Kelly, R. F.: Brit. J. Surg., 1920–1921, **8**, 137.
7. Frishman, E. S.: Brit. Med. J., 1923, **2**, 811.

HYPOGLYCEMIC COMA DUE TO REPEATED INSULIN OVERDOSAGE.

By Elmer L. Sevringhaus, M.D.,

WISCONSIN GENERAL HOSPITAL, MADISON, WIS.

The result of a relative overdose of insulin is usually a sense of uneasiness followed very soon by hunger, warmth of the skin,

perspiration and muscular weakness with a slight tremor. Convulsions and coma are expected to occur in more profound depressions of the amount of circulating glucose. Mental disturbances have not been emphasized as results of hypoglycemia. There are 5 individuals who have been observed in this hospital to suffer an unusual psychic reaction to hypoglycemia. It is not only important to recognize the cause of these conditions in order to properly adjust the dosage subsequently, but it is important to prevent such reactions occurring due to secondary dangers. The striking things in the reactions which these 5 individuals have undergone has been the disorientation and the amnesia. Aphasia and sleepiness seemed to take the place of the common premonition which occurs in most individuals even before hunger, warmth or perspiration have warned the diabetic of a relative overdose of insulin. In all the more severe reactions described there has been no opportunity for the patient to secure assistance.

Case Reports. CASE I.—E. D., a man, aged forty-two years, entered the hospital with a history of diabetes of at least seven years' duration. Insulin treatment with dietary regulation had been tried for a few months in 1923, after which unrestricted diet was used, with no insulin. Weakness and emaciation were progressive, until April 6, 1926, when he was admitted to the hospital, suffering from weakness that was incapacitating. There was edema of the legs, without other demonstrable cause than the diabetic emaciation. In the course of special studies a test meal was given and the fractional gastric samples showed achlorhydria, low-pepsin production and motor function abnormally low. There was no gastric history. On measured diet and insulin therapy he gained weight as expected. At 2 P.M. of the tenth day in the hospital he reported symptoms of hypoglycemia, and was given the usual orange juice, fortified with sucrose. There was no recovery, and nausea began to be apparent. During the course of the two hours following other sugar-containing fluids were given, with eventual relief. The only unusual feature of the episode were the nausea and the marked delay in response to therapy. The noon meal had been taken with the usual relish. The evening meal was similarly enjoyed, and was preceded by insulin. The dosage of insulin was 20 units before breakfast, 15 units before dinner and 20 units before supper. This rate of administration had been unchanged for three days. A hypoglycemic reaction was expected by the patient as well as the staff. Glycosuria had not stopped in any fractional urine specimen until the hour of the reaction. There is good evidence that the doses of insulin were accurately administered. About 8 P.M. the patient was found unconscious by the attending nurse, who had been called by a patient in an adjoining bed. There had evidently been insufficient premonition to enable the diabetic

to ask for any assistance. He was perspiring, and the condition was recognized as probably due to hypoglycemia. Intravenous administration of 3.5 gm. of glucose and oral administration of orange juice were followed by no change. Further glucose administration, together with the intravenous injection of 1 cc. epinephrin and 1 cc. digalen brought a rather prompt return to consciousness. But during this time the patient had vomited large amounts of partially digested food, judged by Drs. Bach and Blount, who were with him, to be the entire evening meal. Much of this was aspirated into the lungs before precautions could be taken to prevent the accident, since vomiting was entirely unexpected. Some of the gastric contents were coughed up, and the patient was soon comfortable and spent a good night. The following day the signs of a bronchopneumonia developed, and he died on the third day from cardiac failure.

At necropsy the findings included bronchopneumonia, which was more marked on the right side, a large, firm, dark liver, a small pancreas with several necrotic areas and an unusually flabby, large stomach, containing recently swallowed food. (Lavage the day before death had removed a very small amount of food; little was eaten after the pneumonia appeared.)

Case II.—R. D., a girl, aged ten years, came to the hospital, October 28, 1923, in a semicomatose condition. Following insulin and dietary treatment, she made a good recovery, and was sent home, November 17, to continue the use of insulin. The dosage was 25, 15 and 10 units before the three meals. This amount had been determined by fractional qualitative tests on the twenty-four-hour urine samples and by blood-sugar determinations to be the maximum tolerated dose without hypoglycemia. Half this dosage was sufficient to prevent glycosuria. It was hoped that maximum dosage would be followed by "pancreatic rest" and increased tolerance. The mother and the patient were experienced in the usual symptoms of insulin hypoglycemia. After the lapse of ten days, the local physician wrote that each day the girl "without warning goes to sleep, and her mother says 'just collapses.' After sleeping about one hour she awakens and feels perfectly well. This sleeping comes on while walking on the street, riding in a car or wherever she may be. Her memory at this time is entirely gone." Following the reduction of insulin dosage, these symptoms disappeared entirely.

Case III.—W. B. was admitted to the hospital on March 6, 1926, in a precomatose condition as a result of dietary excess, omission of insulin and slight upper respiratory infection. While using a diet made up of protein (60 gm.), carbohydrate (60 gm.) and fat (150 gm.), which furnishes 110 gm. "available glucose," it was

found necessary to gradually increase the insulin dosage to 80 units per day before the urine was freed from most of the sugar. The boy denied any accessory food intake or irregularity, and none could be detected. It was found later that there was probably mixing of urine samples by another diabetic patient, which led to the use of unduly large doses of insulin for the boy. As a consequence there were hypoglycemic reactions of the usual type on March 10, 16, 17 and 20, which were relieved promptly by sugar when the nurse was notified. In the afternoon of March 21 he was seen to have an unusually severe reaction, of which he was aware, although he was abnormally boisterous, and was writhing on the bed. The symptoms quickly disappeared following administration of sugar by mouth. Blood taken at this time contained so little sugar that an estimation by the Folin-Wu method was impossible, that is, less than 30 mg. per 100 cc. Later in the evening another mild reaction occurred and was treated as usual. On the following day the boy had no memory of the events which had occurred during the hypoglycemia. Insulin dosage was reduced, but on March 25 an insulin reaction occurred in the afternoon. This led to unconsciousness, in addition to the sweating and weak pulse, before sugar could be given to the patient. Blood sugar at this time was 37.5 mg. per 100 cc. On the following day two reactions occurred: Of the first the patient was aware, and relief came promptly; the second reaction was observed a few hours later with an entire lack of premonition, perspiration or tremor. He was dazed and stuporous, but recovered following sugar ingestion. Since discharge from the hospital the boy has been free from symptoms of insulin reaction, but has been unable to reduce the dosage below the 60 units required at the time of discharge.

Case IV.—L. S., a man, aged thirty-three years, was admitted, February 16, 1926, about seven months after the onset of diabetic symptoms. In order to stop all glycosuria it was necessary to use the evening dose of insulin at 9 P.M. rather than before the supper. Gain in weight was satisfactory, and occasional hypoglycemic reactions of the ordinary type were reported by the patient, following which adjustments of the insulin dosage were effected. After March 16 it was found possible to prevent all but occasional traces of glycosuria with 60 to 65 units of insulin, using a diet of protein (60 gm.), carbohydrate (80 gm.) and fat (190 gm.), which yield 134 gm. "available glucose." There were insulin reactions at intervals of one or two days, until on March 21 there were two. The symptoms at 10 A.M. were as they had been before, but at 7.30 P.M., while sitting in the solarium with other patients he became dazed, could not find his bed and could not reply to questions. A few minutes after receiving sugar he recovered but was unaware of what had happened. There was no perspiration. The following

noon a similar attack occurred just as the tray was brought to the patient, but this time there was profuse perspiration. Relief was secured with orange juice in a few minutes. Insulin dosage was slightly reduced and no further reactions were observed prior to discharge, March 24.

CASE V.—D. M., a girl, aged sixteen years, was first admitted on December 8, 1924, with a diabetic history of about six months' duration. After five weeks in the hospital the condition was sufficiently improved to warrant tonsillectomy. At this time 105 units of insulin were required each day with a diet furnishing only 92 gm. "available glucose." The morning blood sugar was always above 150 mg. per 100 cc., but the urine contained only minimal amounts of sugar. It was not until later that a confession of excess food intake was secured. The excess food had been taken with surprising regularity, judging from the consistency of the picture.

On the day of the operation the noon meal and insulin were given at 10.30 A.M. The meal was eaten, but the other patient in the room reported later that the diabetic patient was very much excited at the prospect of the operation. She dropped off to sleep about noon, and remembered nothing after that. At 1.30 P.M. she talked sleepily to the patient near her. At 1.50 P.M. the nurse found her profoundly comatose. Dr. Bach and Dr. Middleton, who saw her at once, observed profuse perspiration and salivation. There was a suggestion of combative attitude and of resistivity, as in postepileptic states. The use of 1 cc. of epinephrin was followed by some improvement, with a dazed condition for half an hour. In an hour she was entirely normal. Blood sugar in a sample taken after administration of epinephrin was 50 mg. per 100 cc. There is no epileptic history.

Tonsillectomy was subsequently performed, followed by a good recovery. She was discharged, February 6, 1925. During the following eleven months she made indifferent progress, and for some time refused to use insulin or follow the diet. She was rescued from a semicomatose condition, following neglect and infection. In December, 1925, she returned to the supervision of this hospital as an outpatient, attempting to do better. In February another lapse occurred, and she was brought under treatment when dyspnea and drowsiness warned that coma was approaching.

After this she was placed under supervision where coöperation was more certain. Using a diet of protein (50 gm.), carbohydrate (50 gm.) and fat (125 gm.), she remained aglycosuric and gained weight, while taking 65 units of insulin daily. The girl was often slow in movement and rather morose, but no association was made between this and her insulin dosage. About 5.15 P.M. on April 15 she was observed to perspire freely and to be a bit confused. She was unable to reply to questions but obeyed requests to sit

down. When seen by the writer at 5.30 P.M. she could not talk, but could still obey some simple commands slowly. The use of orange juice fortified with sugar gave no signs of improvement in half an hour. There was the same resistivity and the fixity of gaze, suggesting a catatonic state. Intravenous injection of 12 gm. glucose in 50 per cent solution was followed by a change in less than two minutes, and rational conversation in a few minutes. Complete return to normal was slow. On April 20 a similar attack occurred at 8 P.M., relieved likewise by the intravenous injection of glucose. In both these attacks there was complete loss of memory for a period in addition to other evidences of suspended cerebral function. On the days following the occurrences the events in the earlier minutes of the attacks were recalled by the patient as if from a hazy dream. Following the second reaction the insulin dosage was reduced to 40 units daily, with no glycosuria. The mental attitude was greatly improved, suggesting that for some weeks preceding the frank manifestations she had been depressed by a more or less continuous hypoglycemia. The mental improvement has been consistent since the reduction of dosage.

Discussion. It is evident that in Case I the occurrence of hypoglycemia was not merely the result of the increase in glucose tolerance (insulin production), which so frequently is observed after adequate treatment of diabetes is established. The more important factor was the gastric atony, as a result of which so little of the noon and evening meals were absorbed within two hours following ingestion that serious hypoglycemic symptoms developed. The potential danger in such a situation is evident; bronchopneumonia occurred from the aspiration of vomitus during coma. The unusual feature of Case III was the occurrence of the typical "shocks" and the more uncommon reactions where disorientation was such a prominent symptom. The disorientation type of hypoglycemic reaction never occurred until after several of the typical sweating and trembling periods had been experienced at short intervals, and the worst disorientation occurred on the same day that a sweating reaction had also occurred earlier.

In general, the danger of such grave hypoglycemic reactions is not serious, for these periods of disorientation have occurred only when the hypoglycemia has been rather continuous or has been repeated within the course of a day. The usual hypoglycemic reaction is followed by mobilization of glucose from the stores, principally liver glycogen. Possibly the recurrence of hypoglycemia at short intervals exhausts the store of glycogen as does thyroid feeding.[1, 2] With such conditions the hypoglycemia proceeds to depress certain cortical functions, whereas commonly the hypoglycemic process is arrested for some time at levels where only sympathetic and autonomic responses occur. It is striking that convulsions have never

been seen in hypoglycemia in these cases, nor in others in this hospital. Individual variations in the tendency to develop hypoglycemia and the nature of the nervous system's reaction to hypoglycemia in nondiabetic children have been described by Josephs.[3] The study of insulin injection into rabbits has shown that not all rabbits respond to hypoglycemia with convulsions.

Thompson[4] has recently reported 3 patients with symptoms resembling the coma here described. His interpretation of the coma as due to delayed relief from acidosis in the central nervous system would not fit the 5 cases presented, since the coma here described did not come as the immediate sequel to a ketosis. On the other hand, a case has been reported in correspondence by Dr. R. E. van Schaick, in which, following a gastric disturbance, there was ketonuria without glycosuria and coma. The patient, a diabetic who had been using insulin very carefully, was relieved by vigorous administration of glucose, without insulin until glycosuria reappeared. This occurred at least twice within a week. This case showed ketosis as a simple result of fasting. Ketonuria without glycosuria cannot be the evidence of diabetic coma.

It would appear to be the part of wisdom to overdo the matter of antidoting hypoglycemia by the use of excess glucose administration. This can do little harm, and may be of value in preventing a recurrence within a few hours. Not only should revision of the insulin dosage be made at once, but the real cause of the hypoglycemic reaction should be sought for. If it is not apparently an increase of tolerance, such as is now expected in many cases, gastric stasis must be thought of. This may be the cause of poor recovery from glucose therapy or even the cause for secondary trouble, as by vomiting. Since the spontaneous recovery from hypoglycemia involves the hepatic stimulation, and usually the excess production of epinephrin,[1, 2] it appears unwise to try to augment this by the further injection of epinephrin. Some individuals respond poorly to this hormone, and the liver may be unable to respond because of lack of stored glycogen after repeated hepatic stimulation. Epinephrin should be used in emergency situations with hypoglycemia, but it is far safer to have 50 per cent glucose prepared for intravenous use. If the results from oral administration of sugar are not apparent in at most fifteen minutes intravenous glucose appears warranted.

Summary. Hypoglycemic reactions have been observed in five individuals. In each patient the usual type of reaction had occurred at times, but following prolonged hypoglycemia or hypoglycemia repeated at intervals of a few hours the reactions were characterized by disorientation and amnesia, with no premonition sufficient to allow of asking for help. Convulsions did not occur. The dangers in such reactions are mentioned.

BIBLIOGRAPHY.

1. Burn, J. H., and Marks, H. P.: The Relation of the Thyroid Gland to the Action of Insulin, J. Physiol., 1925, **60**, 131.
2. Marks, H. P.: Effect of Thyroid Feeding on Sugar Tolerance, J. Physiol., 1925, **60**, 402.
3. Josephs, H.: Fasting as a Cause of Convulsions, Am. J. Dis. Child., 1926, **31**, 169.
4. Thompson, A. P.: Review of the Later Results of Insulin Treatment, Brit. Med. J., 1926, **1**, 613.

RUPTURED GRAAFIAN FOLLICLE OR CORPUS LUTEUM CYST SIMULATING ACUTE APPENDICITIS.

Review of Cases in New York Hospital Since 1914.

By Elizabeth Brakeley, Ph.D.,

and

Charles E. Farr, M.D.,

New York City.

(From the Service of Dr. Charles L. Gibson at the New York Hospital.)

One of the many mistakes made in the differential diagnosis of acute appendicitis is the finding on operation of a hemorrhage into the abdominal cavity from a ruptured Graafian follicle or corpus luteum cyst. According to the literature, Nélaton, as early as 1851, was aware of this possibility. Novak, of Johns Hopkins, reviewed the literature up to 1917 and found forty such cases. Thirty-six of these had been collected by von Beust in 1914. Ravdin, Hadden, Schumann, Primrose and Wilson have all reported similar cases in which mistakes have been made in the differential diagnosis of cystoma of the ovary where the symptoms and signs pointed strongly to acute appendicitis.

The symptoms most commonly seen were a sudden sharp pain, general over the whole abdomen or referred to the umbilicus, and later becoming localized to the lower right iliac fossa; nausea, frequently vomiting and collapse. There may, or may not, be blood lost per vaginam and the patient may think that she is menstruating. The shock is usually out of proportion to the lesion. On physical examination, the patient appears ill, even acutely ill. The tongue is furred, the face flushed. The knees are usually drawn up in the position of rest. The abdomen is rigid and generally tender with the maximum point of tenderness over the right iliac fossa. The temperature is in the neighborhood of 101° and the pulse is correspondingly elevated. The leukocyte count is high, running from 14,000 to 20,000, somewhat higher than in the average case of appendicitis.

The following is a review of a few of the papers on this subject in recent years:

Wilson, of St. Bartholomew's Hospital, cites a case of hematoma of the ovary simulating an attack of appendicitis. The patient, aged nineteen years, was admitted February 11, 1905. She had been in good health until February 9. The last menstrual period was January 3 to 6. She had felt a sudden pain in the right lower quadrant, first sharp and later becoming dull. She had vomited twice. There had been no vaginal discharge. She had never had "indigestion" although she had been somewhat constipated. Operation showed a hematoma of the right ovary, two inches in diameter, which had ruptured and about an ounce of blood had been lost. Sections through the ovary showed normal ovarian tissue which was infiltrated with blood, and at one edge of the hematoma a mass of luteal tissue. The author has found 5 similar cases of ovarian hemorrhage coming on at or about the time of menstruation. There were 2 cases with the ovary ruptured and a mass of blood in Douglass pouch with localized peritonitis.

In another article a year later, Wilson states: "Ovarian hematomata occur in young people whose pelvic organs are at the height of their functional activity and whose tissues are exceedingly well nourished. They occur in otherwise healthy young women at or about the time of menstruation when the generative organs are gorged with blood and the local blood pressure is high." They frequently occur in patients who are in a state of relatively high sexual excitement. The two cardinal symptoms are abdominal pain and uterine hemorrhage. The pain is caused by the rupture of a follicle and distention of an ovary. He gives this explanation of the process: "As the menstrual period approaches there is an increased flow of blood to the pelvic organs. As a result of this, during the process of ovulation the intraovarian tension rises and forces the enlarging follicle toward the point of least resistance, the periphery of the gland. At a bloodless and thinned-out point on the surface of the ovary, the stigma, the follicle eventually ruptures intraperitoneally. The ovum is discharged together with the degenerative cells of the membrana granulosa. Hemorrhage then takes place into the follicular cavity. . . In normal circumstances a rounded clot is formed filling up the follicular cavity. But occasionally this does not happen and the abdomen has to be opened to stop internal hemorrhage." The author assumes that ovulation takes place at or near the menstrual period, whereas that theory is not at all proven.

Emil Novak, of Johns Hopkins, reviews the cases up to 1917. He says that hematomata were found in 40 out of 85 ovaries removed at operation. They varied in size, some being very small. The largest was 6 cm. in diameter. Most were the result of hemorrhage into a Graafian follicle during the stage of hyperemia just following

the rupture of the follicle. He gives as the forms of ovarian hematomata: (1) Follicular: (*a*) Graafian follicle, (*b*) atretic follicle; (2) corpus luteum; (3) stromal.

The first two were the most common. Regarding the etiologic role of menstruation, he says that hematomata are more commonly found in ovaries removed at a period corresponding to the probable occurrence of ovulation, from the seventh to the sixteenth day of the cycle. The corpus luteum hemorrhage occurred later, the sixteenth to the twenty-fifth day. They have no effect on the character of menstruation. They are frequently associated with pelvic disease.

Primrose, in 1912, reported 2 cases of "Hemorrhage into the Peritoneal Cavity by Accidental Rupture of the Ovary." One was the rupture of a normal Graafian follicle as the result of an accidental strain. The other case was caused by a violent attack of vomiting in an early stage of acute appendicitis. He quotes Hermann as follows: "There is a physiologic bleeding, not enough to give trouble, into the Graafian follicle with ovulation. It has been supposed that this physiologic congestion may, by accidental causes acting shortly before the time of ovulation, be so increased that the bursting of a Graafian follicle will cause bleeding enough to form a hematocele. This is theory. There is no evidence that a healthy ovary ever bleeds enough to form a hematocele."

Schumann, in 1921, stated that the general signs and symptoms are acute pain in one or other iliac fossa, or there may be only a dull ache from pressure of blood; some distention, signs of shock and blood loss; elevation of temperature, moderate leukocytosis, rectus rigidity—the general syndrome of the "acute abdomen." He cites 3 cases of young girls during early menstrual periods who gave all the signs of intraperitoneal hemorrhage. They were not operated upon and all recovered. "Such ovarian hemorrhages are more or less functional errors, that is, an excess of bleeding from the wall of the mature Graafian follicle in an adolescent ovary and there is no demonstrable morphologic change present in the tissues." With more mature women, there is danger of confusion with ectopic pregnancies. When massive hemorrhage takes place from an ovary, there is usually, if not always, to be found some disease of the ovarian bloodvessels. Normal ovaries do not give rise to massive hemorrhage.

In 1923, Ravdin reported a case of ruptured Graafian follicle simulating appendicitis in a girl aged fourteen years. At operation the appendix was found normal. There was a perforated follicle on the posterior surface of the right ovary from which there was active bleeding. Ravdin says that the rupture of a Graafian follicle or corpus luteum may occur just before, during, or just after menstruation. He discusses the theory of the etiology of these hemorrhages.

Hadden reports a case of "Abdominal hemorrhage from ruptured

Graafian follicle cyst" in 1923. The symptoms and signs are very similar to those reported by other authors. There was tenderness and rigidity of the right side of the abdomen but at operation the left ovary was bleeding freely from a ruptured Graafian follicle. The appendix was slightly inflamed. The time of attack was postmenstrual.

Korach, in 1925, stated that it is frequently not possible to differentiate between appendicitis and a follicular hemorrhage from a corpus luteum. He advises operation in cases of doubt.

If an attempt at accurate diagnosis of the condition of ruptured ovarian cysts is to be made, one must consider the most probable time in the menstrual cycle for hemorrhage to take place. Shaw, in 1925, in an article on "The Relation of Ovarian Function to Menstruation," says that the premenstrual changes are first observed about the fourteenth day of the cycle. The cycle is regarded as commencing on the first day of the menstrual discharge. Ovulation in the human female takes place between the thirteenth and the seventeenth days of the cycle. The corpus luteum attains its state of maturity on the nineteenth day and persists in its mature form until about the twenty-seventh day. On the twenty-eighth day and during menstruation the corpus luteum is degenerating.

To summarize the literature, numerous cases are reported which illustrate the difficulty of diagnosis of a ruptured ovarian cyst and the probability of confusion with appendicitis in young girls or with ruptured ectopic pregnancy in older married women. The time of rupture was in all the cases except one in the week preceeding the onset of menstruation, that is, in the twentieth to the twenty-eighth day of the cycle. The ages of the patients were from fourteen to forty years. The signs and symptoms were those of a subacute to an acute attack of appendicitis. The leukocyte count ranged from 10,000 to 34,000, usually higher than that found in the average case of appendicitis. On operation a ruptured Graafian follicle or corpus luteum cyst was found, with hemorrhage into the peritoneal cavity. As far as reported, the patients all made uneventful recoveries.

The following is a series of 13 cases taken from the records of the first surgical, or Cornell division of New York Hospital, service of Dr. Gibson, between the years 1914 and 1925. They illustrate the lack of any one distinguishing feature of cystoma of the ovary, and the difficulty of diagnosis from appendicitis, ruptured ectopic pregnancy or salpingitis. A large number of other cases have been excluded in which at operation were found various complicating features, such as postoperative adhesions or salpingitis. These would have masked the picture of a simple rupture of a cystic ovary. Several cases of supposed cystic ovaries have also been omitted as there was no operation to confirm the diagnosis.

Summary of New York Hospital Cases. 1. Age, eighteen to twenty-eight years.

2. Eight had had previous attacks, including those who had had intermittent attacks for several months before admission.

3. Onset: For those who had ruptured cysts the onset was six hours to four days before admission.

4. Symptoms: (*a*) Pain, usually in the right lower quadrant; 2 had general pain over the whole abdomen; 4 had intermittent pain; 2 had dull aching pain; 3 had pain which radiated up and down the right side, into the back, and down the right leg. (*b*) Vomiting, 4 vomited; 1 had nausea but no vomiting; 4 had no gastrointestinal disturbances. (*c*) Constipation, 3. (*d*) Vaginal discharge, 1. (*e*) Urinary disturbances, 1 had frequency and burning.

5. Signs: (*a*) Tenderness, with 11 tenderness was moderate or marked in the right lower quadrant; 1 had generalized tenderness; 1 had tenderness in the left lower quadrant. (*b*) Rigidity, 5 had rigidity in the right lower quadrant. (*c*) Masses felt, 3.

6. Leukocyte count: 7000 to 46,000; usually 10,000 to 16,000.

7. Menstrual history: Regular and normal, 6; irregular and with pain, 4; periods missed, 2.

8. Relation of menstruation to onset of attack: This was impossible to judge as in some cases the date of onset was several weeks or months before admission. In 5 of the cases the date of the last menstrual period was not given. No. 5 missed her last period which was due one week before onset of attack. No. 6 had onset of attack on fifth day of menstrual cycle. No. 8 had onset on fifteenth day of cycle. No. 10 had onset on twentieth day of cycle. No. 11 had onset on eighteenth day of cycle. No. 13 had onset on twenty-sixth day of cycle.

9. Marital history: Seven married; 1 had 1 child; 1 had had a miscarriage; 6 were single.

10. Temperature and pulse on admission: The temperature ranged from 98.6° to 100.6° F. Pulse ran from 78 to 126.

11. Preoperative diagnosis: Eight appendicitis; 3, cystic ovaries; 3, salpingitis; 2, ruptured ectopics.

12. Result: All recovered.

In addition to these hospital cases, there were 2 private cases, 1 in a multipara, aged thirty years, the other in a girl, aged sixteen years. In the latter an appendectomy had been performed some years previously. Both had a characteristic history and signs of mild peritoneal irritation with pain, nausea, tenderness in the right iliac fossa, and slight rigidity. Both were observed carefully for a period of time when the symptoms gradually subsided and eventually completely disappeared. In the case of the young girl the diagnosis was quite definite for a ruptured Graafian follicle. The time was about the middle of the menstrual cycle. In the older woman without operation, the diagnosis is largely a matter of guess work, but by exclusion it seemed quite probably ovarian hemorrhage.

Conclusions. 1. Small hemorrhages into the corpus luteum, or follicular cysts, are quite frequent. Massive hemorrhages with intraperitoneal bleeding are much more rare.

2. The diagnosis is rather commonly overlooked and appendicitis is usually suspected.

3. With very rare exceptions operative treatment is not indicated.

4. The differential diagnosis is extremely difficult. We have found no pathognomonic sign nor symptom of hemorrhage into the Graafian follicle.

5. In case of doubt observation for a few hours is justifiable but as there is grave danger from delay in appendicitis, and very little danger from an unnecessary exploratory operation, it is wiser to operate if the symptoms do not subside.

REFERENCES.

1. Ravdin, I. S.: Surg. Clinics of N. America, 1923, **3**, 275.
2. Hadden, D.: Am. J. Obst. and Gynec., 1923, **5**, 536.
3. Novak, Emil: Bull. Johns Hopkins Hosp., 1917, **28**, 349.
4. Primrose, A.: Ann. Surg., 1912, **56**, 125.
5. Wilson, Harold W.: Lancet, 1905, **1**, 1196.
6. Wilson, Harold W.: Lancet, 1906, **1**, 1462.
7. Schumann, Edward A.: J. Am. Med. Assn., 1921, **77**, 692.
8. Korach: J. Am. Med. Assn., 1925, **85**, 711.
9. Shaw, W.: J. Am. Med. Assn., 1925, **85**, 854.
10. Greenhill, J. P.: Ruptured Corpus Luteum, Surg., Gynec. and Obst., 1925, **41**, 529.

MYXEDEMATOUS ASCITES REMOVED BY THYROID EXTRACT.

By Harold E. Marsh, M.D.

(From the Jackson Clinic, Madison, Wisconsin.)

The finding of ascites in a woman presenting herself for the relief of progressive enlargement of the abdomen, obviously not due to cardiac disease, would at first suggest some local intraäbdominal lesion. The possibility of such an ascites being directly caused by an endocrine disturbance could be readily overlooked, especially since the rarity of such a condition is evidenced by the paucity of references in the literature.

Report of Case (39121). Mrs. A. E. P., aged thirty-seven years, came to the Jackson Clinic, February 1924, complaining chiefly of an enlargement of the abdomen. Eighteen months previously she first noticed swelling of her hands, feet and jaw. Coincident with this her skin assumed a yellowish pallor, and she began to slow down physically, so that her duties became irksome and it was an

effort for her to get about. She believed that her circulation was poor as her feet became cold and numb very readily. Six months before she came to the Clinic her abdomen began to increase in size, and associated with this was a bearing down sensation in the lower abdomen. Exertion produced moderate dyspnea, and she found that she could rest more comfortably at night with two pillows. The appetite remained good. The patient always suffered with severe headaches at the time of menstruation, but with the onset of her illness the headaches ceased. Her menstrual period stopped December, 1923. It has been necessary for her to pass her urine seven or eight times during the day and twice at night.

The appearance of this patient gave the impression of late pernicious anemia or nephritis. Her entire face was puffy, especially under the eyes, and had a yellowish pallor. The mucous membrane of the mouth was pale; the tongue was thick and beefy, and the teeth showed evidence of much repair work. Small cervical glands were palpable on both sides of her neck. The heart and lungs were normal. The skin of her body was dry. The abdomen was protuberant and symmetrical; no mass could be felt on palpation but a distinct fluid wave was discernible. There were no dilated superficial veins. Pelvic examination was unsatisfactory due to the large amount of abdominal fluid. There was a slight edema of the lower legs and feet; the hands were puffy but would not pit on pressure. The systolic blood pressure was 118; diastolic, 80; pulse, 88; and temperature 98°. A single specimen of urine revealed nothing but an occasional pus cell. Examination of the blood showed hemoglobin 55 per cent, erythrocytes, 4,290,000; leukocytes, 8200; and a normal differential count.

A diagnosis was not made, and the patient was sent to the hospital for observation.

The combined renal functional test showed a 50 per cent return of the dye. The blood urea was 59 mg.

February 5, a small incision was made below the navel and 3 gallons of yellowish fluid were removed. Exploration showed a normal spleen, liver, pelvis and peritoneum. February 13, a transfusion of 400 cc. of blood was given and this was repeated on the nineteenth. Two days later the hemoglobin was 72 per cent, and erythrocytes, 3,400,000.

The ascites gradually returned to almost its former degree. The swelling of the face, hands and feet remained the same and the patient noticed very little change in her general condition.

February 29, the basal metabolic rate was found to be minus 37 per cent. Three days later she was given 10 mg. of thyroxin intravenously. Four days following this she had a severe systemic reaction with generalized aching and chills. Improvement within a few days was very noticeable and progressive. Her mentality, which had been very sluggish, became more alert, and she could

talk and think more rapidly. Her skin began to scale and for the first time in months she felt warm and perspired slightly. The systolic blood pressure rose to 140.

March 15, the basal metabolic rate had risen to minus 14 per cent. The size of the abdomen had decreased appreciably and the edema of the face, hands, and feet was much less marked. Five days after this, a second dose of 10 mg. of thyroxin was given intravenously with a reaction on the following day, but this was much less severe than that following the first administration.

March 26, the basal metabolic rate was + 7 per cent and treatment with 2 gr. of thyroid extract three times a day was commenced. The blood count at this time revealed hemoglobin 69 per cent and erythrocytes 5,390,000. Early in April the ascites had entirely disappeared and the edema of the face, hands, and feet had cleared up. Her skin was moist and warm, and she was feeling very much stronger and more alert both physically and mentally. The middle of April she started to menstruate for the first time in four months. Administration of thyroid extract was reduced to 2 gr. twice daily.

In September, her basal metabolic rate was + 2 per cent and she had gained 24 pounds. Her hair which had become gray at the onset of her trouble began to turn to its normal brown color. She felt well in every way.

The basal metabolic rate in January, 1925, was + 9 per cent, hemoglobin, 70 per cent and erythrocytes, 5,200,000.

The following summer she discontinued the thyroid tablets for two weeks and her face became puffy and pale. As soon as the thyroid was resumed these conditions disappeared.

In June, 1926, her basal metabolic rate was plus 2 per cent; she was feeling well, and the results of examination were negative. She had been taking 2 grains of thyroid extract twice daily.

Discussion. Fournier[1] has observed elsewhere and in his own practice 5 cases of myxedema with ascites and edema; in 2 of these hydrothorax appeared in the course of the myxedema. The 3 patients who were treated by him were women between twenty-five and forty years of age who had never been troubled with cardiac, hepatic or tuberculous affections. The administration of thyroid extract was always followed by marked diuresis and within two to five weeks the thyroid insufficiency and the dropsy syndrome disappeared. Fournier does not give the report of any metabolism studies on these patients. He refers to a case of ascites and myxedema, reported by Nothnagel, which was completely cured by the administration of thyroid extract.

Fournier states that the action of thyroid extract on dropsy syndromes which develop independent of thyroid insufficiency is undeniable but is inconstant and rapidly loses its power. On the

contrary, when thyroid extract is administered to a patient with a dropsy syndrome which has developed on a myxedematous basis, the action of the drug is constant and lasting. He believes in the existence of a dropsy syndrome produced entirely by thyroid insufficiency. In the absence of anatomic proof, he advances a hypothesis.

Ascites associated with myxedema which persists until thyroid extract is administered and then entirely disappears would appear to be caused and kept up by the thyroid insufficiency. Myxedema is not an uncommon disease, and if it can cause ascites we would expect to find the two associated more frequently. Myxedema, however, may make it possible for some other condition to arise which is directly responsible for the ascites and when the thyroid insufficiency is cured the other factor may no longer be able to produce the fluid. Until we are able to dissociate myxedema and ascites in these cases we must consider one as being the cause of the other.

REFERENCE.

1. Fournier, M. J.: Syndrome hydropigène et insuffisance thyroïdienne, Bull. Acad. de med., Paris, 1925, **93**, 691.

THE TREATMENT OF HAY FEVER WITH EPHEDRIN.*

PRELIMINARY REPORT.

BY FRED W. GAARDE, M.D.,

AND

CHARLES K. MAYTUM, M.D.,

DIVISION OF MEDICINE, MAYO CLINIC, ROCHESTER, MINN.

EPHEDRIN is the active substance obtained from ma huang, a plant which has been used in medicine in China for many centuries. It was first isolated in 1887 by Nagai,[3] while in recent years Chen has made detailed studies of its physiologic and pharmacologic action as related to modern medicine. Chen and Schmidt,[1] Miller,[2] Thomas[5] and Rowntree and Brown[4] have made carefully controlled observations on the action of ephedrin, and have demonstrated its similarity in general effect to adrenalin. As pointed out by Miller, ephedrin has the advantage that it is effective when given by mouth as well as by hypodermic injection, and also that the action of a single dose may persist for hours.

It was our original intention to make a study of the effect of this drug on bronchial asthma, and in so doing treated a few cases which

* Submitted for publication, May 19, 1926.

were associated with ragweed fever. The effect on the hay-fever symptoms was rather striking and, since the supply of ephedrin was limited, it was decided to take advantage of the season and treat hay-fever patients only. The ephedrin used was made in the laboratories of Peking Union Medical College, under the method of K. K. Chen.

Treatment. Twenty-six patients with active hay fever of the autumnal type were treated with 60-mg. doses of ephedrin, given orally in capsules. Because of our limited experience with the drug, the patients were instructed to use it only during severe attacks and to take not more than 2 or 3 capsules in twenty-four hours. Each patient, therefore, used from 5 to 10 capsules each week while under treatment. Most of the patients complained of slight nervousness, increase in pulse rate and tremor soon after the medicine had been taken. To some this proved a very objectionable feature while others did not mind it. The toleration of the drug from this standpoint seemed largely dependent on the neurotic temperament of the patient. The observers previously mentioned gave doses up to 200 or 250 mg. daily with comparatively infrequent subjective manifestations. This difference in reaction is probably due to the fact that their studies were made on bed patients or at least on patients under proper control, while our patients were active and engaged in their regular duties. For the same reason, our report deals entirely with the amount of symptomatic relief, since it was impossible for us to keep satisfactory record of blood-pressure, pulse rate and so forth.

Results. Results are classified as good, fair and negative. Of the 26 patients, 13 obtained complete or almost complete relief from symptoms for from three to seven hours after each dose. Excessive nasal secretions stopped, ocular symptoms disappeared and in every way the patients were entirely comfortable. The youngest patient, aged ten years, maintained comfort by taking 20 mg. for his morning paroxysm, whereas previously he had had several paroxysms each day. One patient, with mild symptoms, used ephedrin only before going for a drive or before attending a social function, and was always able to spend several hours in perfect comfort.

In 5 cases the result was fair, and partial relief was obtained for two or three hours after each dose. Symptoms did not entirely disappear, but, as expressed by 1 patient, were alleviated sufficiently to warrant the use of ephedrin. We have included in this group 2 cases in which splendid results were obtained with 60-mg. doses, the patients preferring the partial relief produced by 30 mg. to the "nervousness" caused by the larger dose. In 8 cases results were negative; little or no benefit was received. We have placed in this group 3 patients of neurotic temperament who refused to take more than their first dose because of the subjective symptoms produced.

In summarizing the results we made an effort to determine why some patients responded to treatment and why some did not. Failure was encountered only in very severe cases—those in which bronchitis was associated and those in which the temperament was extremely neurotic. The good results were obtained in the moderately severe and milder cases. About half of the 26 patients had received preseasonal desensitization injections of ragweed with only partial benefit. This fact apparently did not influence the result obtained except when it had mitigated the symptoms. In 2 severe cases in which no improvement had followed preseasonal injections of pollen no relief was caused by ephedrin. It is possible that more careful control of the patient and variation in dosage will give better results in these severe cases.

Comment. We have found it difficult to determine accurately the value of ephedrin in the treatment of hay fever because of the limited number of patients and because they were ambulatory and difficult to control. Also, hay-fever symptoms are paroxysmal in nature, and it is possible that on some occasions the drug was administered toward the end of an attack. However, there was a sufficient number of patients with continuous symptoms, and those with paroxysmal symptoms were treated under sufficiently variable circumstances and over a long enough period to warrant the conclusion that ephedrin will fill a definite place in the symptomatic treatment of hay fever. Further experience and better control of patients should improve the results.

BIBLIOGRAPHY.

1. Chen, K. K., and Schmidt, C. F.: Action of Ephedrin, the Active Principle of the Chinese Drug Ma Huang, J. Pharm. and Exper. Therap., 1924, **24**, 339.
2. Miller, T. G.: A Consideration of the Clinical Value of Ephedrin, with a Report on its Effects in Certain Special Cases, Am. J. Med. Sci., 1925, **170**, 157.
3. Nagai: Quoted by Miller.
4. Rowntree, L. G., and Brown, G. E.: Personal communication.
5. Thomas, W. S.: Ephedrin in Asthma, a Clinical Report, Am. J. Med. Sci., 1926, **171**, 719.

DUODENAL DIVERTICULUM.

With Report of a Case Associated with Definite Symptoms.

By R. H. Kampmeier, B.A., M.D.,
ANN ARBOR, MICH.

(From the Department of Internal Medicine, Medical School, University of Michigan.)

Diverticulum of the duodenum is a relatively rare clinical finding, but is of importance since it may have clinical manifesta-

tions. Of the various portions of the duodenum, the first portion is the most infrequent as a site for diverticulosis. In the case to be reported, there was found a fairly large pouch, arising from the first portion of the duodenum, and associated with it, a definite group of symptoms.

Frequency of Duodenal Diverticulosis. In 1911, Baldwin[1] stated that there were less than 100 reported cases of diverticulosis, including all portions of the duodenum, in the literature. He, himself, added 15 more cases found at autopsy. Diverticulosis had been considered to be merely of anatomical interest, until it was demonstrated that the lesion could be visualized by the Roentgen ray examination; and further, that this lesion could be of clinical significance. All authors accredit the first roentgenologic demonstration of duodenal diverticulum to Case, who presented a series of 4 cases in the Scientific Exhibit of the American Medical Association in 1913. In 1916, this author (Case[2]) reported 7 cases found by him in the routine Roentgen ray examination of the gastrointestinal tract. Subsequently, in 1920, Case[3] reported a total of 85 cases found in 6847 barium-meal examinations. In the years preceding this latter report, series consisting of a few cases each, were reported by other authors. Groover and Christie[4] reported 8 cases in 1300, and Watkins[5] 4 cases in 1000 examinations. Recently Hartung[6] published 8 cases of duodenal diverticulosis found in 1500 barium-meal studies. Case, as well as Hartung, places the incidence of duodenal diverticulosis, including all portions of the duodenum, at about 1 per cent of roentgenologic gastrointestinal examinations.

Anatomy and Pathology. In his 15 cases, Baldwin found that in 2 the sac was in the first portion, in 7 in the second portion and in 6 in the third portion of the duodenum. Case[3] places the distribution in his 85 cases as follows: 17 in the first portion, 49 in the second portion, and 19 in the third or duodenojejunal portion. Cole and Roberts[7] state that only 3 per cent of all duodenal diverticula are situated in the first portion. All authors call attention to the relative frequency of this lesion in the second portion, where many of them are related to the ampulla of Vater.

Diverticula of the duodenum are usually found singly, less commonly they are multiple. In size, duodenal diverticula are reported as varying from that of a pea to dimensions of 4 to 5 cm. in the largest diameter. Diverticula may be round, pear-shaped, or tubular, and may communicate with the lumen of the duodenum by a small opening or one continuing the diameter of the sac.

Although there are great differences of opinion with respect to the etiology of duodenal diverticula, the majority of authors subdivide them into congenital and acquired. The term "true diverticulum" is used by some to designate those whose walls contain all coats; whereas, "false diverticulum" is applied to those lacking the muscular coat. Certain authors state that true diverticula

are congenital, and conversely, that false ones are acquired. Cole and Roberts[7] review the various theories as to the etiology of this lesion, and the reader is referred to their publication for this résumé. Some believe the pouch may be congenital, as: (1) Offshoots from the gut to form a supernumerary pancreas, (microscopically bits of pancreatic tissue are commonly found incorporated in the wall of the sac); or (2) as a weakness in the duodenal wall, which later allows herniation. The latter explanation seems valid, because the great majority of duodenal diverticula appear in patients past middle age, at which time a certain amount of elasticity of the bowel wall is lost. These authors also call attention to the large group of acquired "inflammatory" or "pseudodiverticula" which have been produced as a result of preëxisting pathology, such as, ulcer, pancreatitis, cholecystitis, and the like. Such lesions are associated with adhesions which may lead to distortion, and traction diverticula of the duodenum.

Diagnosis. All authors agree that the diagnosis of duodenal diverticulum cannot be made clinically. There is no typical, or even suggestive symptom complex. In a certain number of patients there has been a syndrome simulating peptic ulcer, chronic cholecystitis, pancreatitis, or there have been indefinite complaints referred to the epigastrium. Some authors, even, do not accredit the diverticulum with being responsible for the symptoms of which the patient may be complaining. Without exception, the diagnosis is made during a barium meal examination, as an accidental finding, while searching for a cause of the patient's complaints.

Case Report. M. D., female, white, aged thirty-six years, a clerk. The patient entered the Medical Out-Patient Department of the University Hospital, complaining of pain in the epigastrium, and general weakness.

Present Illness. The patient had had more or less trouble with the stomach for the past twenty-four years. As a child of twelve years, she had repeated attacks of "catarrh of the stomach." For the past several years, she had noted pain coming on two to four hours after meals. The pain was dull in character, associated with a sense of fullness in the epigastrium. Pain was confined to the epigastric region and did not radiate. Food, bicarbonate of soda, pressure applied to the epigastrium, or lying on the face, would relieve the pain. Five years ago there was hematemesis consisting of fresh blood. Tiredness from work aggravated the symptoms.

In the last three months before the patient presented herself at the Clinic, the pain had been more constant, though of the same character. In addition, there had been constipation, headache, weakness, anorexia, and a loss of 20 pounds of weight in this period. There had been no nausea or vomiting.

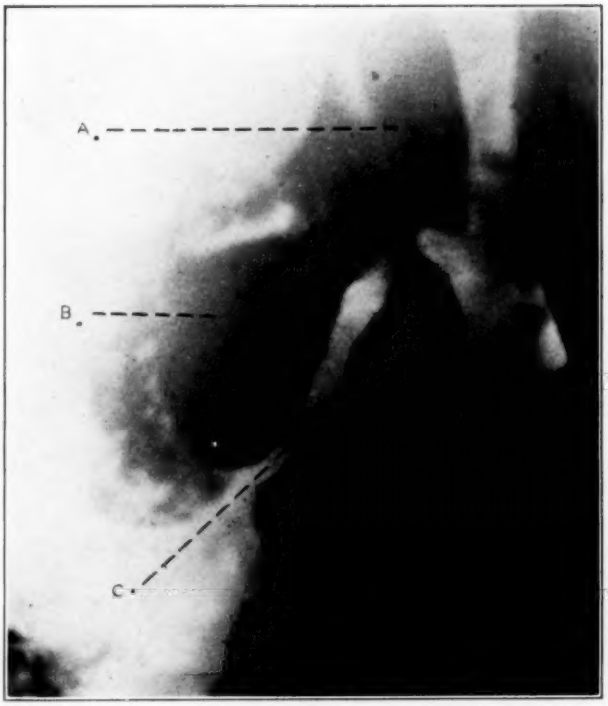


FIG. 1.—Roentgenogram. (*A*) First portion of duodenum; (*B*) diverticulum arising from first portion of duodenum; (*C*) pylorus.

Physical Examination. The patient appeared to be moderately well nourished, with no loss of skin elasticity; she did not appear acutely ill. With exception of the abdomen, the examination was essentially negative. The abdomen was scaphoid, and presented a panniculus of about 2 cm. There was epigastric tenderness, and some muscle resistance in the right upper quadrant. The blood Wassermann and the urine were negative.

Roentgenologic Examination. The patient was referred to the Department of Roentgenology with a tentative diagnosis of duodenal ulcer. The report of this department is as follows: "Fluoroscopically there was no demonstrable abnormality of thorax or stomach. The opaque meal, upon passage through the stomach into the duodenum, filled readily into a large pouch, descending from the greater curvature of the bulb. This was smooth in contour and could be easily emptied by manipulation, but filled again at the advent of the next peristaltic wave. The second portion of the duodenum was demonstrated as lying above and to the left of this pouch. At six hours the stomach was empty, the diverticulum still retained some of the barium meal and was demonstrated on films taken at this time. At twenty-four hours the diverticulum was empty and the barium meal was in the colon."

The patient was operated upon under ethylene anesthesia. The operative report is as follows: "Upon opening the peritoneal cavity, the gall bladder was found at the level of the umbilicus. The stomach was not low as compared to the gall bladder. Though the gall bladder was enlarged, it seemed normal and emptied easily. No pathology was found in the stomach. Just below the pylorus was found a pouchlike diverticulum of the duodenum. When dilated it seemed to be about 1½ inches in diameter. It had a wide neck opening into the duodenum. The pylorus was patent. There was slight scarring on the anterior surface of the neck, but this was not marked. The diverticulum was easily mobilized, there were no dense adhesions, and excised at the neck." Postoperative recovery was uneventful, and the patient was discharged on the sixteenth postoperative day.

The pathologic report is as follows: "The duodenal diverticulum shows marked chronic catarrh with localized hyperplasia and atrophy of the mucosa. In the submucosa and through the muscularis are patches of inflammatory fibrosis. All coats of the wall are present, and there is no pancreatic tissue."

Summary. Diverticulosis of the duodenum has been found in about 1 per cent of cases in extensive series of barium-meal studies, occurring usually in patients past middle age. Only about 3 per cent of these occur in the first portion of the duodenum. Clinically, duodenal diverticulum cannot be diagnosed, being, without exception, found at Roentgen ray examination.

The above case was reported because of the rarity of diverticulum of the first portion of the duodenum. The pouch was found to be of comparatively large size, and contained all coats in its wall. Because of the fact that the sac could be so easily emptied by manipulation during the fluoroscopic examination, it may be considered probable that this lesion was never associated with very extensive inflammatory pathology. This is further borne out by the fact that the pouch was easily mobilized at operation, and was found to have only a few adhesions. Finally the case was thought to be of interest because of the comparative youth of the patient, and especially because of its association with a clinically definite group of symptoms.

REFERENCES.

1. Baldwin, W. M.: Duodenal Diverticula in Man, Anat. Record, 1911, **5**, 121.
2. Case, J. T.: Roentgen Observations on the Duodenum with Special Reference to Lesions beyond the First Portion, Am. J. Roentgenol., 1916, **3**, 314.
3. Case, J. T.: Diverticula of Small Intestine, other than Meckel's Diverticulum, J. Am. Med. Assn., 1920, **75**, 1463.
4. Groover, T. A., and Christie, A. C.: Analysis of 1300 Cases Referred for Gastro-intestinal Study, with Special Reference to the Importance of Chest Examination of Such Cases, Am. J. Roentgenol., 1919, **6**, 571.
5. Watkins, W. W.: Pathological Findings in One Thousand Roentgen ray Examinations of the Digestive Tract, Am. J. Roentgenol., 1920, **7**, 234.
6. Hartung, A.: Diverticula of the Duodenum, Radiology, 1925, **4**, 308.
7. Cole, L. G. and Roberts, D.: Diverticula of the Duodenum, Surg., Gynec. and Obst., 1920, **31**, 376.

REVIEWS.

Osler's Modern Medicine. Volume III. Edited by Thomas McCrae, M.D. Pp. 1052; 51 illustrations. Philadelphia: Lea & Febiger, 1926. Per set of six volumes, $54.00.

The volume begins with an excellent chapter on metabolism from the point of view of the practitioner, the opening chapter of the Section on Diseases of Metabolism. Then follow articles on diabetes mellitus and insipidus, gout and obesity. Part II of the book includes a discussion of diseases of the digestive tract. Many of the articles have been rewritten by those who contributed to earlier editions. Of particular note is the chapter on diseases of the esophagus by Jackson and Clerf. The volume keeps up the high standard of those which have preceded. R. K.

Diseases of the Ear, by Adam Politzer. Revised by Milton J. Ballin. Sixth edition; pp. 776, 302 illustrations. Philadelphia: Lea & Febiger, 1926. Price, $10.00.

Politzer's book on the ear has long been regarded as a classic It might be said that it bears the same relation to otology as Osler's work to internal medicine. The authors and publishers have done well to make again available this work which was practically out of print. Fortunately few changes have been made, the changes being of subtraction rather than addition. Illustrations of obsolete instruments and text that is no longer of value have been omitted. K. H.

A Manual of Bacteriology, Clinical and Applied. By R. Tanner Hewlett, M.D., F.R.C.P., D.P.H. (Lond.), F.K.C., F.R.M.S., Emeritus Professor of Bacteriology, University of London; Director of Pathology, Seaman's Hospital, Greenwich; Lecturer on Bacteriology, School of Hygiene and Tropical Medicine. Eighth edition. Pp. 645; 38 plates and 63 figures. London, J. & A. Churchill, 1926.

During the twenty-eight years since the appearance of the first edition of this manual its text has mellowed into the classic under repeated revision. The present edition reflects the keenness, accuracy and life-long experience of a great teacher of science. The

inclusion of accounts of the bacteriophage, Bacterium pneumosintes; the Kahn precipitation test in syphilis; the Dick test in scarlet fever; the work of Gye and Barnard in malignant disease—all attest the care and thoroughness exercised in bringing the text up to date. Important chapters on the protozoa are included.

The plates and text illustrations are excellent. The book includes so many commendable features that one cannot indicate all in brief review. Some features of the technique of the British methods will not appeal to American teachers, but these are more than compensated by the broadening effects of an appreciation of the viewpoint of the British school in their application. This is a valuable book for student, teacher and practical worker. J. S.

GASTRIC FUNCTION IN HEALTH AND DISEASE. By JOHN A. RYLE, M.D. (LOND.), F.R.C.P., Assistant Physician and Lecturer on Medical Pathology, Guy's Hospital. Pp. 152; 6 tables, 26 charts and 2 illustrations. London: Humphrey Milford, Oxford University Press, 1926. Price, $2.75.

THE author has summarized in this little book the present-day working knowledge of the functions of the stomach. Originally given by him as Goulstonian Lectures in 1925, this presentation in book form serves the purpose of making his contribution more generally available. Included in it are some interesting data on test-meal studies made in his own clinic. His classification of the common dyspepsias into habit, nervous or psychogenic, toxic and infective, irritative and mechanical is cumbersome and overlapping, but at least shows how complicated the matter is and how meager our knowledge of gastric disturbances still is. T. M.

AN INTRODUCTION TO THE STUDY OF ROENTGEN RAYS AND RADIUM. By HECTOR A. COLWELL, M.B., Director of the Radiological Department, King's College Hospital Medical School, University of London; and CECIL P. G. WAKELEY, F.R.C.S. (ENG.), Assistant Surgeon, King's College Hospital. Pp. 203; 37 illustrations. London: Humphrey Milford, Oxford University Press, 1926. Price, $3.35.

THE scope of this book is indicated by its title, and the authors have in an unusual way presented an extremely technical subject in a simple style. This book should be most acceptable to teachers and students alike, and particularly to roentgenologists. The text is divided into twelve chapters and an appendix, discussing them

as follows: The Cathode Particles; the Roentgen Rays; Induction Coils, Transformers, etc.; Certain Forms of Roentgen Ray Examination; The Preparation of Radium Salts; The Preparation and Measurement of Radium Emanation (Radon); The Action of Radiations on Normal Tissue; Some Notes on Roentgen Ray and Radium Therapy; Some Facts and Theories Concerning the Mode of Action of Radiation upon Living Tissues; The Atomic Theory; Protection Methods and the Protection Committee's Report. In the appendix Fundamental and Derived Units, Notes on Index Notation and some Anatomic Landmarks are explained. E. P.

THE DIAGNOSIS, TREATMENT AND END RESULTS OF TUBERCULOUS DISEASE OF THE HIP JOINT. By GEORGE PERKINS, M.Ch. (OXON), F.R.C.S. (ENG.), Assistant Surgeon to the Royal National Orthopedic Hospital, Assistant Surgeon to Pyrford Orthopedic Hospital, Orthopedic Registar, St. Thomas's Hospital. Pp. 117; 32 illustrations. London: Humphrey Milford, Oxford University Press, 1926. Price, $1.75.

IN this very interesting and instructive volume the author presents present-day knowledge of the diagnosis, differential diagnosis and general treatment of this important subject. The author endeavors to present the main facts of the subject and especially the primary importance of recognizing the condition early and the means to prevent deformity. The text gives a complete survey of the condition in the different phases and the importance of the open-air treatment and heliotherapy. The book contains many original instructive illustrations. As a whole, the author presents a very practical treatise. D. W.

DISEASES OF THE NEWBORN: A MONOGRAPHIC HANDBOOK. By JOHN A. FOOTE, M.D., Professor of Diseases of Children, Georgetown University Medical School, including chapters by PRENTISS WILSON, M.D., JAMES M. MOSER, M.D., WILLIAM F. O'DONNELL, M.D., FREDERICK J. EICHENLAUB, M.D., and JOHN F. O'BRIEN, M.D. Pp. 231; 85 illustrations and 2 charts. Philadelphia: J. B. Lippincott Company, 1926. Price, $5.00.

THIS work considers the newborn in a simple orderly fashion acceptable to the practitioner and intern. It is as the author indicates, a handbook and not a treatise. Injuries are well discussed, especially intracranial hemorrhage. A section on diseases commonly seen in the newborn is useful. The skin affections are

especially well covered. It is regretted that more consideration has not been given to artificial feeding of the newborn and to pylorospasm and pyloric stenosis. The book is handsomely printed and is generously illustrated. J. S.

PYGMALION, OR THE DOCTOR OF THE FUTURE. By R. M. WILSON, M.B., CH.B. Pp. 67; 12 mo. New York: E. P. Dutton & Co., 1926. Price, $1.00.

THE sprightly "Today and Tomorrow" series, of which *Pygmalion* is the latest representative, might well have included "yesterday" in its scope, at least as far as its titles are concerned. Who among us does not have to brush up his mythology to comprehend the significance of Dædalus, Icarus, Narcissus, Tantalus, Callimicus, Hypatia, Perseus and Prometheus—not to name a dozen more promised soon to appear? It is not amiss then to recall that Pygmalion was the Cyprian misanthropic sculptor who fell in love with his own statue of Venus, which was brought to life in response to his prayer and made him break his vow never to marry. How is the myth applied to the doctor of the future "in the fatness of these pursy times?" The reader must almost finish the book before he reaches the answer.

The medical purpose of the booklet is to elaborate the theory that "symptoms are signs not of reaction to disease, but of altered reaction to life, occasioned by the presence of disease," and it is therefore very appropriately dedicated to the memory of Sir James McKenzie. Although the author implies a much narrower and less satisfactory meaning of "symptom" than is usually understood by the term—no actual definition being given—nevertheless in the author's sense we will grant that his thesis is mainly true, especially for such symptoms as pain. It is difficult, however, to comprehend how the anesthesia due to a cord tumor, for instance, is anything but a reaction to or the result of disease, unless the argument is pursued to a point where it becomes a distinction without a difference. The argument loses none of its force, however, by not being applicable to all symptoms, and is certainly an instructive and important application of McKenzie's studies, which should be mastered by all those who aim to treat their patients as well as their ailments. Interesting also is the author's vision of the doctor of the future as a humanist, understanding human nature and human motives, a man of culture, lover of the arts as well as student of the sciences. With the simplification of medical science which is bound to follow the present era of exuberant expansion, this is an attainment possible and devoutly to be hoped for. E. K.

ABDOMINAL OPERATIONS. By SIR BERKELEY MOYNIHAN. Fourth edition, revised. Two octavo volumes. Pp. 1217; illustrated. Philadelphia: W. B. Saunders Company, 1926.

THE author of this work needs no introduction to readers of surgical subjects. The fact that this work has gone to the fourth edition is proof of its value. We all know the high position in which the writer stands. This work owes its value not only to the presentation of the various indications for, and methods of operation upon, abdominal pathology, but even more so to the unparalleled personal experiences. As quoted in the preface, it has often been stated that succeeding editions of a work should be smaller than the earlier ones. This is not the case in this instance, despite the fact that much has been omitted, the cause having been found to be obsolete. Chapters have been added on the operating-room technique and the preoperative care of the patient. The reviewer considers these two chapters of inestimable value. The old dictum of "Cut well, sew well, get well" in modern surgical parlance reads "Cut well, sew well, treat well, get well."

It has not been the reviewer's privilege for many years to read a book that has appealed to him as much both from the standpoint of surgical meat as well as literary perfection as does this work. It reads like a novel, yet at the same time transfers to the reader the wonderful personality of the writer. E. E.

EXPERIMENTAL PHARMACOLOGY AS A BASIS FOR THERAPEUTICS. By HANS H. MEYER and R. GOTTLIEB. Second edition, in English, translated from the seventh German edition by Velyien E. Henderson. Pp. 656; 89 illustrations. Philadelphia: Lippincott & Co., 1926. Price, $7.00.

HALSEY'S translation of the second German edition of this book has long been out of print and Professor Henderson is to be thanked for having again made it available in English. The arrangement of subject matter, unique among textbooks of pharmacology, is the same as in earlier editions. To the physician who wishes to refresh his understanding of the physiology with which he deals when he uses drugs in the treatment of disease, this discriminating and authoritative book should be invaluable. It should be of the greatest usefulness to medical students in that perplexing transition which they undergo when, after two years spent in the study of the so-called fundamental sciences, they turn to the clinical study of disease and its treatment. A. R.

BOOKS RECEIVED

Medical Gymnastics and Massage. By DR. J. ARVEDSON. Translated and edited by MINA L. DOBBIE, M.D., B.CH. Second edition. Pp. 284. Philadelphia: P. Blakiston's Son & Co., 1925. Price, $2.50.

The Human Cerebrospinal Fluid. VOL. IV. ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASE. Pp. 568; 77 illustrations. New York: Paul B. Hoeber, Inc., 1926. Price, $10.00.

The Surgical Treatment of Goiter. By WILLIAM BARTLETT, A.B., A.M., M.D., D.Sc., F.A.C.S. Pp. 365; 130 illustrations. St. Louis: C. V. Mosby Company, 1926. Price, $8.50.

Practical Materia Medica and Prescription Writing. By OSCAR W. BETHEA, M.D., PH.G., F.C.S. Fourth edition. Pp. 498. Philadelphia: F. A. Davis Company, 1926. Price, $4.50.

Dietetics for Adults and Children in Health and Disease. By SANFORD BLUM, A.B., M.S., M.D. Second edition. Pp. 362. Philadelphia: F. A. Davis Company, 1926. Price, $4.00.

Diseases of Children. By HECTOR CHARLES CAMERON, A.M., M.D. (CANTAB.). Pp. 199. New York: Oxford University Press, American Branch, 1926.

Duodenal Tube and Its Possibilities. By MAX EINHORN, M.D. Second edition. Pp. 206; 126 illustrations. Philadelphia: F. A. Davis Company, 1926. Price, $3.00.

Brain and Heart. By GIULIO FANO. Translated by HELEN INGLEBY. Pp. 142; 19 illustrations. New York: Oxford University Press, American Branch, 1926.

Pathology and Treatment of the Inflammatory Diseases of the Nasal Accessory Sinuses. By PROF. DR. M. HAJEK; translated and edited by JOSEPH D. HEITGER, A.B., M.D., and FRENCH K. HANSEL, M.D., M.S. Fifth edition. Two volumes. Pp. 702; 186 illustrations. St. Louis: C. V. Mosby Company, 1926. Price, $17.00.

Radiotherapy in Relation to General Medicine. By FRANCIS HERNAMAN-JOHNSON, M.D. Pp. 211. New York: Oxford University Press, American Branch, 1926.

A Manual of Proctology. By F. CHITTENDEN HILL, PH.B., M.D., F.A.C.S. Second edition. Pp. 294; 101 illustrations. Philadelphia: Lea & Febiger, 1926. Price, $3.50.

Plastic Surgery of the Head, Face and Neck. By H. LYONS HUNT, M.D., L.R.C.S. (EDIN.). Pp. 404; 352 illustrations. Philadelphia: Lea & Febiger, 1926. Price, $7.00.

A Laboratory Manual for Elementary Zoölogy. By LIBBIE HENRIETTA HYMAN. Pp. 182. Chicago: University of Chicago Press, 1926.

Diagnose und Therapie. By DR. S. JESSNER. Pp. 173. Leipzig: Curt Kabitzsch, 1926.

The Diabetic Life. By R. D. LAWRENCE, M.A., M.D. Second edition. Pp. 167; 11 illustrations. Philadelphia: P. Blakiston's Son & Co., 1926. Price, $2.50.

Defective Memory, Absentmindedness and Their Treatment. By ARNOLD LORAND, M.D. Pp. 340. Philadelphia: F. A. Davis Company, 1926.

Cannula Implants and Review of Implantation Techniques in Esthetic Surgery. By CHARLES CONRAD MILLER, M.D. Pp. 178; 11 illustrations. Chicago: The Oak Press, 1926. Price, $2.00.

Electrothermic Methods in the Treatment of Neoplastic Diseases. By J. DOUGLAS MORGAN, B.A., M.D. Pp. 172; 36 illustrations. Philadelphia: F. A. Davis Company, 1926. Price, $2.50.

Laboratory Outlines in Bacteriology and Immunology. By JOHN F. NORTON, PH.D., and I. S. FALK, PH.D. Pp. 114. Chicago: University of Chicago Press, 1926.

The Surgery of Gastroduodenal Ulceration. By CHARLES A. PANNETT, B.SC., M.D. (LOND.), F.R.C.S. (ENG.). Pp. 154; 55 illustrations. New York: Oxford University Press, American Branch, 1926.

Methods and Problems of Medical Education. Fifth Series. Pp. 225; illustrated. New York: Division of Medical Education, Rockefeller Foundation, 1926.

A Practice of Physiotherapy. By C. M. SAMPSON, M.D. Pp. 620 146 illustrations. St. Louis: C. V. Mosby Company, 1926. Price, $10.00.

Das Autonome Nervensystem. By DR. MED. ERICH SCHILF. Pp. 207; 25 illustrations. Leipzig: Georg Thieme, 1926.

The Treatment of Fractures. By CHARLES LOCKE SCUDDER, A.B., PH.B., M.D., F.A.C.S. Tenth edition. Pp. 1240; 2027 illustrations. Philadelphia: W.B. Saunders Company, 1926. Price, $12.00.

Die Tierischen Parasiten des Menschen: II. Klinik und Therapie der Tierischen Parasiten des Menschen. By OTTO SEIFERT. Pp. 574. Leipzig: Curt Kabitzsch, 1926.

Essays in the History of Medicine. By KARL SUDHOFF, M.D. Translated by various hands and edited by FIELDING H. GARRISON, M.D. Pp. 397; 6 illustrations. New York: Medical Life Press, 1926. Price, $5.00.

Surgery of Neoplastic Diseases by Electrothermic Methods. By GEORGE A. WYETH, M.D. Pp. 316; 137 illustrations. New York: Paul B. Hoeber, Inc., 1926. Price, $7.50.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

ROGER S. MORRIS, M.D.,

TAYLOR PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Treatment of Pernicious Anemia by a Special Diet.—At a recent meeting of the American Medical Association one of the papers presented which caused an unusual amount of discussion was that of MINOT and MURPHY. This paper has now appeared (*J. Am. Med. Assn.*, 1926, **87**, 470) in print. It should certainly prove a help in carrying the ideas of these two authors to those who did not have the opportunity of hearing the original presentation. They report 45 patients with pernicious anemia who were treated by a special form of diet. They report that there is a distinct, prompt and rapid diminution of the anemia, together with marked symptomatic improvement following the institution of this dietetic treatment. The rise in the blood count was really quite phenomenal and was brought about apparently entirely by dietetic treatment. This diet is rich in iron and purin derivatives. The exact diet is as follows: (1) From 120 to 240 gm., and even sometimes more, of cooked calf or beef's liver. An equal quantity of lamb's kidneys was substituted occasionally. (2) One hundred and twenty grams or more of beef or mutton muscle meat (3) Not less than 300 gm. of vegetables containing from 1 to 10 per cent of carbohydrate, especially lettuce and spinach. (4) From 250 to 500 gm. of fruit, especially peaches, apricots, strawberries, pineapple, oranges and grapefruit. (5) About 40 gm. of fat derived from butter and cream, allowed in order to make the food attractive. However animal fats and oils were excluded so far as possible. (6) If desired, an egg and 240 gm. of milk. (7) In addition to the above-mentioned

foods, bread, especially dry and crusty, potato and cereals, in order to allow a total intake of between 2000 and 3000 calories composed usually of about 340 gm. of carbohydrate, 135 gm. of protein and not more than 70 gm. of fat. Grossly sweet foods were not given, but sugar was allowed very sparingly. This diet is apparently very well borne, according to the observations of the authors, together with confirmatory evidence of men who have used the diet according to the author's plan.

The Austin Flint Phenomenon: An Experimental and Clinical Study.—HERRMANN (*Am. Heart J.*, 1926, **1**, 671) presents an interesting discussion of this phenomenon seen in aortic regurgitation As is well known, there has been considerable discussion as to the explanation of the apical diastolic murmur which was first described by Flint in 1861 and which, incidentally, was first noticed by him in a patient dying at the old Charity Hospital at New Orleans. As a result of experimental work on animals and autopsy studies of human cases, the author has come to the conclusion that the mechanism of production of the Flint murmur depends upon a functional mitral obstruction of this valve. Cases in which this murmur has been well marked have shown at autopsy that the lesions were most marked in the posterior aortic cusp and that when experimental aortic disease is produced in animals when the posterior cusp is severely injured by the valvotome, the murmur of Flint was most likely to be produced. As a result of involvement of the posterior cusps, the regurgitant stream of blood spends its force against the anterior mitral flap and drives this flap into the mitral orifice, because the regurgitant aortic pressure is higher than that of the left auricle, producing a functional obstruction or stenosis. The vibration of the anterior mitral segment results in the murmur that is heard in the apex. This contention of the author as to the explanation of the Austin Flint phenomenon is not original, but it has been very largely discarded for other theories as to the causation of the condition. However, the author is the first to bring very definite clinical proof or any experimental evidence to substantiate his explanation.

The Origin of Malignant Tumors.—BLUMENTHAL (*Deutsch. med. Wchnschr.*, 1926, **52**, 1284) has found that cell-free fluids from human patients suffering from cancer (edema fluid and pleural exudate) can under certain circumstances produce cancer in rats, which, however, was rat and not human cancer. This suggests a similarity to the tumor-exciting principle of the filtrate of Rous' chicken sarcoma, and makes the author believe that the three strains of bacilli (resembling each other in form and pleomorphism but differing in agglutination reactions) that he has cultivated from many types of human cancer are not the causes of cancer, so much as carriers of its exciting agent like the insect carriers of pathogenic protozoa. He suggests that these and other cancer excitants, such as tar, arsenic and indol (Carrel) may either activate a latent contagium vivum or stimulate body cells to elaborate substances which produce tumor formation. The original article should be consulted for a lucid correlation of the work of Gye, Carrel, Warburg and many others on the biologic aspects of malignant neoplasms.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE MEDICAL SCHOOL AND ASSOCIATE PROFESSOR OF SURGERY IN THE SCHOOL FOR GRADUATES IN MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL AND NORTHEASTERN HOSPITALS.

Gastric Motility.—KLEIN (*Arch. Surg.*, 1926, **12**, 1224) states that acidity on the gastric or duodenal side of the pylorus does not normally control the activity of that sphincter. Fluidity of the chyme in the antrum is the factor of prime importance for its expression. Solid bodies, which by chance get into the antrum, are carried back into the body by retrograde peristalsis. Each advancing peristaltic wave overcomes the tone of the pylorus and forces some of the chyme into the duodenum, regardless of whether the reaction of the chyme is neutral, acid or alkaline. The period of expression of the chyme during which the pylorus is open occupies a greater part of the gastric cycle than the period in which it is closed. In other words, the pylorus is open for a longer time than it is closed. The pyloric tone normally only keeps the sphincter closed when the pressure on either side is insufficient to overcome it. This is one type of pyloric closure. It is overcome, on the one hand, by each advancing gastric wave and, on the other hand, may be overcome by retrograde peristalsis in the duodenum resulting in intestinal regurgitation. Firm decisive closure of the pylorus occurs at the termination of each peristaltic wave when the latter has reached the sphincter and after it has forced the chyme into the duodenum. It effectually prevents any regurgitation. The latter closure always occupies the same proportion of time in the gastric cycle.

Rectal Pathology Caused by Syphilis.—MONTAGUE (*Am. J. Syph.*, 1926, **10**, 254) writes that primary syphilis of the anorectal region is much more frequent than the older published data would indicate. Anal chancres are more common than rectal, but both are overlooked, often being regarded as ordinary fissures in ano. There is, however, in the chancre much more induration with accompanying enlargement of the inguinal glands. Examination of a scraping from the ulcer under the dark-field microscope is a very definite means of arriving at a diagnosis. The employment of this method is one reason for increasing recognition of the occurrence of primary lesions in the anorectal tissues. The commonest secondary manifestation of syphilis in the anorectal tissues is the formation of condylomas. They consist of wart-like flat papillomas arising from the skin. The skin itself is freely movable, indicating that the process does not extend to a greater depth than the cutaneous layer. The only other secondary manifestation is the presence of mucous patches in the rectum. By far the most frequent and most characteristic tertiary manifestation of syphilis in this region is that of gummatous inflammation, most frequently found as

round or oval swellings in the submucosa of the rectum. They are quite painless. Discrete formations do not lead to stricture. In diffuse forms, however, the rectal wall immediately surrounding them is stiff and leathery and the natural and frequent sequel to this process, extending as it does over a long period of time, is a stricture of the rectum.

Some Interesting Problems in Renal Surgery.—BUGBEE (*J. Urol.*, 1926, **15**, 431) says that hematuria, however slight, may be of extreme importance, and should never be passed over without thorough and repeated study. By such means renal tumors will be diagnosed much more often, and in their incipiency, when a cure may be possible. Renal tuberculosis presents many and varied types—the more chronic forms being probably often misunderstood. Nature develops remarkable resistance to this type of infection. Such resistance should be utilized to the fullest in the handling of these cases. Anomalous renal vessels as a cause of ureteral obstruction and resulting hydronephrosis are more common than has been previously believed to be the case. Pyelography in these cases may give a fairly definite picture. Temporizing in such cases is of no avail. Renal calculi call for a most careful study of each case, the best judgment in outlining the proper procedure to be followed and careful operative technique. Conservation in deciding upon operation, the proper preparation of the patient for operation, conservation of kidney tissue, nephrotomy preliminary to nephrectomy in poor surgical risks, the free employment of transfusion and intelligent after care will go far toward placing kidney surgery in its proper place as one of the most interesting, accurate and satisfactory branches of surgery.

The Trigone of the Bladder as a Factor in Urinary Obstruction.—HUNNAN and WESSON (*Surg., Gynec. and Obst.*, 1926, **43**, 1) say that hypertrophy of the interureteral ridge may result from chronic vesical irritation, from mild types of vesical or infravesical obstruction or from both in combination. These hypertrophies of the interureteral ridge may be of a type and in a position to produce in themselves obstruction to urination. An obstructing interureteral bar or ridge is always an acquired condition though the cause may be congenital. An obstructing interureteral ridge may also result from chronic ulceration, usually tuberculous, which has led to a dissected or undetermined trigone. Marked obstruction from a hypertrophied ridge seems to be due principally to the hydrostatic undermining of the trigone back of it, a position practically immune to the formation of diverticuli. The treatment of an obstructing interureteral ridge is surgical by suprapubic cystotomy, and either incision of the ridge with suture and ligature of the incised edges to control hemorrhage or resection of the ridge and the supratrigonal pouch with restoration of the base of the bladder, which is the preferable method when these pouches are deep. Before operation for an hypertrophied interureteral ridge, in case it has been secondary to obstruction, the primary obstruction should first be removed and a period of time allowed to elapse, so that it may be seen whether the removal of the original obstruction will not cause a disappearance of the interureteric hypertrophy.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,

OF PHILADELPHIA.

Chemical Changes in the Body Occurring as the Result of Vomiting.—HARTMANN, SCOTT and MOSER (*Am. J. Dis. Child.*, 1926, **32**, 1) found that as a result of vomiting chlorid is lost. As chlorid diminishes in the blood, bicarbonate is retained and compensates at least in part for the deficiency in electrolyte, so that the total salt concentration still remains about normal. When the loss of sodium chlorid in the blood is not fully replaced by sodium bicarbonate the nonprotein nitrogen becomes elevated, to the extent of keeping osmotic pressure normal—theoretically at least. When the sodium bicarbonate content of the blood is high there is a depression of respiration sufficient to lead to the accumulation of enough carbonic acid to maintain an approximately normal H_2CO_3 to $NaHCO_3$ ratio, so that the reaction of the blood is usually almost normal. Following increased pulmonary ventilation from any cause the blood becomes abnormally alkaline and the manifestations of tetany may appear. When the deficiency of sodium chlorid in the blood disappears as a result of the administration of sodium chlorid the excess of nonprotein nitrogen and sodium bicarbonate in the blood is rapidly excreted by way of the urine. Excretion of sodium bicarbonate, sodium chlorid and nonprotein nitrogen depends on the total concentration of crystalloid or electrolyte and nonelectrolyte in the blood. When this concentration is less than normal sodium bicarbonate is retained in the blood and the urine remains acid in reaction despite the presence of a greatly increased plasma carbon dioxid content. Marked vomiting without actual organic pyloric or intestinal obstruction may also lead to identical chemical changes. Loss of gastric or intestinal secretion by way of fistulas results in the same chemical changes as does vomiting.

The Metabolism of Salts in Nephritis—Calcium and Phosphorus.—BOYD, COURTENAY and MCLACHLAN (*Am. J. Dis. Child.*, 1926, **32**, 29), as a result of their research, report that the blood phosphates were increased in 66 per cent of the nephritic serums examined. Blood calcium was decreased in 71 per cent. The calcium and phosphates in the blood in nephritis bear an approximately reciprocal relationship to each other. High blood phosphates were usually found in patients with acidosis, but were also noted in some patients with no acidotic symptoms. Symptoms or signs of nephritis other than acidosis did not appear to bear any direct relationship to the level of the blood calcium phosphate. Serum phosphates are apparently of some prognostic value in nephritis, when transitory rises due to acidosis are excluded. A persistent moderate increase indicates that there is present a progressive renal lesion. High blood phosphates have a prognostic value comparable to high blood creatinin except when

acidosis is present. Nephritic children have a positive calcium balance unless their intake falls to a low level, slightly higher than the minimal on which normal children have a positive balance. The difference is probably due to better absorption in normal children on more bulky diets. The nephritic kidney is functionally incapable of excreting calcium in a normal manner. This is evidenced by the low concentration in the urine. The calcium balance is apparently independent of the blood calcium content. The presence or absence of edema plays an important part in the phosphate balance. Nonhydremic subjects have a negative balance in most cases, and extraneous factors explain the exceptions. Edematous subjects have a positive balance, except occasional cases with a minimal intake. The evidence of phosphate retention given by blood and balance studies does not always agree. The daily excretion of phosphates in nephritic patients compares favorably with that of the normal. The percentage of the intake found in the urine in the pathologic subjects often exceeds that in the healthy subjects. The phosphate concentration of the urine is usually within normal range. In those in whom it was found strikingly decreased the blood phosphates were always very high. Variations in the calcium intake did not influence the proportion of phosphate excreted by the urine or bowel.

The Diagnosis of Incipient Tuberculosis in Children.—Donnelly and Riesman (*Arch. Pediat.*, 1926, **43**, 386) state that the prevalence of a positive tuberculin test is not as universal as was formerly believed. In a child under ten years of age this is of great significance and should be given due consideration. Usually a persistent negative tuberculin reaction indicates the absence of a tuberculous infection. Excluding tuberculous lesions of the bone and other organs, tuberculosis in children is essentially a tracheobronchial adenitis, with little or no discernible physical signs except a positive d'Espine. The presence of enlarged tracheobronchial glands does not necessarily mean tuberculosis and a negative tuberculin reaction is of great aid in differentiation. Children with incipient tuberculosis are not necessarily underweight. There is not a greater incidence of tuberculosis infection among malnourished school children. The role that bovine tuberculosis plays in tuberculosis has been greatly exaggerated with small realization as to the importance of human contagion. A definite history of contact, the presence of enlarged tracheobronchial glands and a positive tuberculin test are sufficient evidence upon which to make a diagnosis of incipient tuberculosis in children.

Splenic Disease, with Special Reference to Splenectomy in Children.—Kuhn (*Arch. Pediat.*, 1926, **43**, 407) indicates that the spleen, although its function may not be fully understood even at the present time, may best be considered as a filter placed in the blood stream under normal conditions to filter the red blood cells that disintegrate daily. The spleen is very aptly called the graveyard of the red blood corpuscles. Under pathologic conditions cells foreign to the circulation, such as nucleated red cells, myelocytes, bacteria and other toxic

agents, are also filtered out, the retention of which adds greatly to the increase of the size of the organ. Splenectomy, generally speaking, is contraindicated in the leukemias and pernicious anemia. In Gaucher's disease and von Jaksch's anemia removal of the spleen should be undertaken only after the greatest deliberation. In many cases of Banti's disease, congenital family hemolytic jaundice and purpura hemorrhagica splenectomy is definitely indicated. It is firmly established that the spleen is not necessary to life and the improvement in surgical technique has transferred the treatment of many of its diseases to the field of surgery.

Feeding of Children.—Müller (*Med. Klin.*, 1926, **22**, 795) is strongly opposed to the overfeeding of children with milk. In the second and third years 400 gm. a day is sufficient. Between the seventh and the tenth years 300 gm. and later 250 gm. are a good average daily intake. Milk contains more fluid than is required. Dried milk might be advantageous. Children should be given about 20 gm. of meat or liver daily in the second year; 40 gm. in the fourth year; 60 gm. in the eighth year, and up to 100 gm. at puberty. Blood is a valuable food. About one-sixth to one-third of an egg yolk, preferably raw, is recommended for children over one year of age every other day. Older children may have two or three eggs but not more per week. Bread is an important source of protein as well as of carbohydrates. Crackers and pastries made from the finest flours should be avoided. Vegetables and fruits are necessary. It is irrational to boil the potatoes in water and thus extract the salts, unless the water is used for vegetables. It is useless and harmful to force the child to take soup; concentrated bouillon in small quantity is enough.

Pneumococcus Types in Pneumonia in Children.—Westlund (*J. Infect. Dis.*, 1926, **38**, 514) examined 69 cases of lobar pneumonia and 34 cases of bronchopneumonia in children between the ages of three weeks and eleven years. He obtains pneumococci by nasopharyngeal swabbing in 60.8 per cent of the cases of lobar pneumonia and in 52.6 per cent of the cases of bronchopneumonia. The relative incidence of pneumococcus types in these two groups was much the same, Group 4 predominating, Type II coming next in frequency, Type I third and Type III being least frequent. The fixed types of pneumococcus are less frequent in the pneumonias of children than in those of the adults. The association of Group 4 with one or another of the fixed types was demonstrated in several instances. In a group of 13 cases of non-pneumonic respiratory disease in children pneumococci were present in 92 per cent. No examples of Types I and III were encountered, Type II and Group 4 forming one-third and two-thirds, respectively, of the isolated pneumococci. In 48 nonrespiratory diseases in children pneumococci were found in 58 per cent. Type I was not represented in this group; Type II formed 14.2 per cent; Type III, 3.6 per cent; Group 4, 82.1 per cent. The occurrence of Type II pneumococcus in the throats of these children in the hospital wards may have been due to contact.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY AT THE SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA,

AND

CLEVELAND J. WHITE, M.D.,

ASSOCIATE IN DERMATOLOGY AND SYPHILOLOGY, UNIVERSITY OF BUFFALO, BUFFALO, N. Y.

Ultraviolet Light in the Treatment of Roentgen Ray Telangiectases.—LANE (*Arch. Dermat. and Syph.*, 1926, **13**, 237) was able to produce definite obliteration of Roentgen ray telangiectases by the ultraviolet light with pressure. No results were secured in the atrophic, pigmented or scarred portions of Roentgen ray residues. The patient was a young woman who had had numerous Roentgen ray treatments, both filtered and unfiltered, for a tuberculous cervical adenitis. The dosage used was three and a half to four and a half minutes with pressure, with the water-cooled quartz lamp, or enough to produce flaccid vesiculation. Proper intervals should be observed both between areas treated at a given time and dates of successive treatments. The author warns of the seriousness of traumatizing a tissue already atrophic and degenerative, and the treatment should be undertaken with great caution, with a full knowledge of the abnormality of the tissue which is being treated, and with great care to prevent infection of the bullæ and erosions produced by the treatment.

Syphilitic Alopecia: Its Relation to Neurosyphilis.—WILE and BELOTE (*Arch. Dermat. and Syph.*, 1926, **13**, 495) make an important contribution to the knowledge of the types of alopecia in early syphilis and their probable clinical importance. They differentiate syphilitic alopecia into two distinct types—the essential and the symptomatic. In a study of 37 cases, 30 were found to be of the former type and 7 of the latter. Alopecia of the essential type has a high associated incidence of meningeal neurosyphilis, as indicated by spinal-fluid findings, there being only 3 cases out of the 30 in which these findings could be construed as being entirely negative. The absence of changes in the spinal fluid cannot, however, be accepted as absolute evidence of the absence of neurosyphilitic involvement; in fact, one negative case had definite neurosyphilis as indicated by clinical findings. In the essential type of alopecia there were no visible skin manifestations on the scalp or in the associated patchy losses of hair found quite frequently on other parts of the body. Histologic study of the denuded areas showed that there was no local pathologic disturbance of the follicular apparatus. Clinical analogy affords the suggestion that the essential type of alopecia is due to endocrine dysfunction as a result of associated involvement of the autonomic nervous system. Symptomatic alopecia is accompanied or caused by an exanthem of the scalp, the histologic picture showing a

perivascular and perifollicular syphilitic plasmonia in each case. Five cases out of the 7 of this type were frankly negative to neurologic examination and the spinal-fluid findings, and the other 2 showed very slight changes. A further interesting observation was the association of leukoderma colli with the essential type of alopecia, there being 11 instances of leukoderma in the 30 cases of essential alopecia, while there was only 1 in the symptomatic group. Clinical differentiation between the two types depends on the moth-eaten appearance without other cutaneous lesions in the essential type, and the same moth-eaten appearance plus the papular syphilid in the symptomatic group.

Large-spored Ringworm Infection of Beard and Scalp—Treatment with Foreign Protein Injections.—ENGMAN (*Arch. Dermat. and Syph.*, 1926, **13**, 352) reports the cure of large-spored ringworm infection of the beard in 2 men and of the scalp in 3 children by intravenous injections of suspensions of typhoid bacilli. The doses in the men varies from an initial 50,000,000, gradually increasing to 300,000,000; in the children from 7,000,000 up to 250,000,000. Injections were given every four to five days; a reliable commercial product was used. Cures resulted within a month's time in the men, while the children cleared up on the average of two months. The author feels that the injections should be large enough to produce a marked systemic effect as well as a rise in temperature. This method is contraindicated in delicate persons and in those with organic disorders, especially nephritic patients or those with cardiac conditions. The small-spored ringworm infections do not respond to this method of treatment.

OBSTETRICS

UNDER THE CHARGE OF

NORRIS W. VAUX, M.D.,

CLINICAL PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA,

AND

CLIFFORD B. LULL, M.D.,

CLINICAL ASSISTANT IN THE OBSTETRICAL DEPARTMENT, JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

Oviduct Insufflation Based on a Study of Four Hundred Cases.—RONGY (*Am. J. Obst. and Gynec.*, 1926, **11**, 616) believes that insufflation of the oviduct is now utilized as a routine measure to establish definitely their patency under the technique developed by Rubin and those who follow him. The author has studied 400 cases, making the examination about seven days after menstruation, because at that time the genital tract is less congested and there is a greater chance for the gas to pass through without causing disturbances. His cases were fluoroscoped to see the gas in the abdominal cavity. The average

rise of the mercury column in patients whose tubes were open was 131 mm., and in patients in whom the tubes were closed it was 197 mm. He seldom allowed the mercury column to rise above 220 mm. As contraindications to the procedure, he lists pain and tenderness in the pelvic region, severe leukorrheas, unless they were carefully cleansed, and patients who suffer from extreme obesity and cardiac disease. The complications to be feared are pelvic infection and syncope attacks that may be even fatal. Oviduct insufflation has helped to crystallize further our knowledge of sterility in women. Operations on the cervix, intracervical stem pessaries and even plastic operations upon the Fallopian tubes for the cure of sterility can be discarded as of no value. In this series of 400 cases the patients ranged between twenty-two and forty-one years of age, the average was twenty-seven and two-fifth years and the average time of marriage was six and two fifth years. The tubes were found patent in 225 cases. In a few cases the tubes were found closed at the first examination, but patent at a reëxamination. Ninety-nine patients who suffered from primary sterility had severe menstrual disturbances; in all these cases the tubes were found patent. In 142 cases the tubes were found closed. The majority of these patients suffered from relative sterility and gave a history of infection which evidently had developed insidiously as a result of childbirth or miscarriage. Three patients in whom the oviducts were found closed became pregnant subsequently, so that prognosis must be guarded. It is possible that spasm of the tubes prevented the passage of gas when no actual obstruction existed. Oviduct insufflation is of great diagnostic value in patients in whom we suspect a chronic pelvic infection. Its therapeutic value is doubtful. It is a safe procedure in properly selected cases.

Blood Pressure and Urinary Findings in One Hundred Cases of Normal Pregnancy.—Faught (*Am. J. Obst. and Gynec.*, 1926, **11**, 633) states the general teaching that systolic blood-pressure readings above 130 mm. of mercury are abnormal and that the presence of albumin, casts and red blood cells in the urine indicate kidney deficiency are held by him to be erroneous in pregnancy. He has studied the blood pressure and urinary findings in 100 cases of normal pregnancy in his private practice; most of the cases were studied from the third month, a few from the fifth week of pregnancy. None of the cases developed permanent damage to the cardiovascular or renal systems subsequent to delivery. Their ages ranged from eighteen to forty-one years. Of a total of 675 urinalyses, 44.1 per cent showed albumin alone or with other urinary abnormality. Twelve per cent of primiparæ showed no albumin in the urine throughout the pregnancy, while 7 per cent showed albumin in all their urine examinations. Of the multiparæ, 10 per cent showed no albumin and 5 per cent always had albumin in demonstrable quantity in the urine. The albuminuria occurred with slightly greater frequency in primiparæ than in multiparæ. Glycosuria was not unusual in pregnancy, occurring in 4.3 per cent of all specimens examined, being present most frequently in the sixth, seventh and eighth months. The percentage of glucose was rarely over 1.5 per cent. The incidence of indican was slightly greater than glucose, occurring in 11.1 per cent

of all specimens examined; frequently it was associated with glucose. The systolic blood pressure ranged between 190 and 80 mm.; 11.5 per cent of all cases showed a systolic blood pressure over 130 mm. of mercury. The pulse pressures were quite uniform, though slightly greater than those considered usual in normal subjects. The author does not consider the mere elevation of systolic blood pressure is an indication of the approach of grave complications.

A Classification of the Toxemias of the Latter Half of Pregnancy.—STANDER and PECKMAN (*Am. J. Obst. and Gynec.*, 1926, **11**, 583) state that, considering the present method of classification of the toxemias of the latter half of pregnancy as admittedly inadequate, they have correlated the findings in a series of 120 patients presenting one or other types of the toxemias of pregnancy. The differential diagnosis was not made until the third week of the puerperium, and in doubtful cases final diagnosis was not made until six weeks after delivery, when the patient was subjected to clinical and chemical investigations. Their ultimate classifications were: (1) Eclampsia: A fairly definite entity with convulsions, coma, greatly elevated blood pressure and a large amount of albumin in the urine, occurring during the last third of pregnancy but more frequently near term, and a complete return to normal at the end of the puerperium; there was no evidence that eclampsia *per se* did permanent damage to the kidney and shall not be considered a contraindication for further conception. (2) Pre-eclampsia: This differed from eclampsia only insofar as the patient had no convulsions nor coma and the attack may be of a milder character; this was the rarest type of toxemia. (3) Chronic nephritis complicating pregnancy: This group is characterized by the usual findings of a chronic nephritis exaggerated by the pregnancy and persisting after the termination of the pregnancy; the process is progressive, the manifestations become more marked and usually appear earlier in the course of subsequent pregnancies. (4) Low kidney reserve: During the last few months of pregnancy these cases show a moderate rise of blood pressure and a relatively small amount of albumin in the urine; there may be some edema and rarely a complaint of headache; these symptoms subside by the end of puerperium. In subsequent pregnancies a similar picture may recur but this type of kidney is not injured by pregnancy. A series of charts are presented, showing the findings in each case, under its group classification.

Injuries of the Infant during Delivery.—BLAND (*Am. J. Obst. and Gynec.*, 1926, **11**, 477) in this full and very comprehensive article has carefully covered the entire field and the conclusions drawn from a study of a number of cases of injuries of the infant during delivery is, in a large number of instances, preventable. The means of prevention he groups under two headings: (1) A wide adoption and higher standard of prenatal care; (2) a more thorough intranatal study and training and better practice.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Diathermy Treatment of Gonococcal Endocervicitis.—The successful treatment of gonococcal endocervicitis by any method other than surgical removal of the diseased structures has always been a problem. Although cauterization is frequently successful, it must be admitted that it is more or less mutilating and is often followed by the formation of dense scar tissue. In order to obtain the effect of intense heat without its destructive action on the tissues, WALTHER and PEACOCK (*South. Med. J.*, 1926, **19**, 202) have applied diathermy with gratifying results. They describe in detail the technique which they used, and insist that it must be rigidly followed if good results are to be obtained. Of their 38 cases, 12 were acute and 26 chronic, the number of treatments per case varying from 2 to 14. The duration of the average treatment was ten minutes and the average milliampèrage used was about 500. The control of the discharge was usually noted after the first treatment. They believe that the treatment of gonococcal endocervicitis has been much simplified by the use of diathermy which effectually destroys the gonococcus *in situ*, leaves no scar tissue, materially shortens the time usually required for treating such cases, is painless in its application and is clean.

Cancer Survey in Massachusetts.—The results of an investigation into the cancer situation in Massachusetts in 1925 have been presented by NICHOLS, GOODHUE, CHAMPION, BIGELOW and LOMBARD (*Boston Med. and Surg. J.*, 1926, **194**, 388). They find that cancer is on the increase, but there are indications that the peak of the curve may be nearly reached. Massachusetts has the highest death rate of any state in the union. The proportionate mortality for cancer among inmates of almshouses and insane institutions is lower than among the general population of the same age distribution. The cancer rate increased with density up to a population of about 4000 per square mile. From there it remains nearly stationary. The cancer rate increases from west to east in Massachusetts. The average duration of life for patients operated upon for cancer who die of cancer is 22.8 and for patients not operated upon, 20. The average during from onset to operation is ten and three-tenths months. The average patient comes to a doctor eight months after first noticing symptoms. About one-fourth of all cancer deaths occur in hospitals, but the length of stay in hospitals is too short to be considered adequate. The hospitals are increasing their share of the cancer load. There is need for additional

beds for cancer cases as well as for all chronic diseases. While Roentgen ray and radium facilities are available for ambulatory cases, in many localities they are not available for bed cases.

Incidence of Cancer in the Cervical Stump.—In every discussion which takes place concerning the relative values of the supravaginal and total hysterectomy, the chief point which is made by the proponents of the total operation is that the retained cervical stump is apt to undergo malignant change and, therefore, had better be removed together with the fundus, claiming that the risk of the total operation is very little greater than that of the supravaginal hysterectomy. We have always maintained and we believe that a careful perusal of the facts will substantiate our claim that the total operation has a distinctly higher mortality, whereas, the risk of malignant change in the retained cervix is a negligible one. An interesting study of this possibility has been made of the material of the Woman's Hospital in New York by HOCHMAN (*Am. J. Obst. and Gynec.*, 1926, **11**, 566), who finds that in the series of 1114 supravaginal hysterectomies at the Woman's Hospital, 3, or 0.27 per cent, developed subsequent carcinoma of the stump. In a series of 263 cases of carcinoma of the cervix, 7, or 2.66 per cent, had had a supravaginal hysterectomy for a nonmalignant condition, at which time 4 of the 7 cases were most likely coëxistent, leaving only 1.14 per cent truly subsequent cases of carcinoma. In 377 of the operations with coning out of the cervix, 1, or 0.26 per cent, developed carcinoma of the cervical stump. In 595 of the operations with carbolization of the stump, 2, or 0.33 per cent, developed future malignancy. Coning out of the cervix helps prevent future infection and, in a great measure, future carcinoma of the cervical stump. This technique takes no more time than carbolization, which does not even prevent infection, much less cancer, and should be adopted as a routine in supravaginal hysterectomy. The occurrence of carcinoma in the stump of the cervix does not warrant a panhysterectomy, with its much greater mortality. In the above series 1111 cervices would have needlessly been removed, with the loss of the keystone of the arch and complications, resulting from a disturbance of the pelvic anatomy. Moreover, even panhysterectomy does not give assurance of freedom from future malignancy. Where a definite pathologic cervix which is lacerated or infected, especially where discharge is present, exists at the time of the supravaginal hysterectomy, it should be removed then or as soon as possible. All cases after a supravaginal hysterectomy should have an adequate follow-up system with definite periodic examinations for any changes in the cervix and for any history of bleeding or discharge. This is extremely important for the early detection of carcinoma, with favorable prognosis by early treatment, especially radiation. A very careful examination should be made of the cervix at the time of operation (hysterectomy) to decide whether the cervix should be removed with the uterus, and if not in all doubtful cases a sufficient amount should be excised for pathologic examination. This is especially important where any degeneration or necrosis exists in the uterus.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

DEWAYNE G. RICHEY, B.S., M.D.,

MERCY HOSPITAL, PITTSBURGH, PA.

A Method for the Experimental Production of Lung Abscess.—Because recent studies in other types of postoperative lung complications would seem to indicate that emboli from the operative field were the dominant factor in the ensuing complication, HOLMAN, WEIDLEIN and SCHLUETER (*Proc. Soc., Exper. Biol. and Med.*, 1926, **23**, 266) felt that lung abscess might have a similar etiology. Accordingly, a previously produced embolus of infected tissue was introduced into the right jugular vein of 17 dogs, under ether anesthesia. A definite lung abscess was produced in 12 of the 17 attempts. In 15 instances the embolus lodged in the left lower lobe, and only twice in the right lower lobe—facts explained on an anatomic basis by the authors. Of the 5 cases in which an abscess failed to develop, 2 showed evidences of a healing infarct at autopsy. In 3 animals the roentgenograms showed no evidence of abscess formation, and the dogs have remained well. The investigators believe that the method of producing lung abscess may be the means of furnishing further experimental evidence in favor of the embolic theory of lung abscess. Retrospector's Note.—These results are intensely interesting, especially in view of the observations of other workers, such as Fetterolf (*Laryngoscope*, 1922, **32**, 517, and AM. J. MED. SCI., 1923, **166**, 802 and Myerson, abstracted AM. J. MED. SCI., 1925, **170**, 619.)

Aural Auscultation.—In certain therapeutic procedures for conditions of the middle ear and Eustachian tube, such as inflation per catheter, it is customary for the otologist to employ a "diagnostic" tube consisting of a single piece of rubber tubing which connects the patient's ear with his own ear. ROSENBLATT (*Illinois Med. J.*, 1926, **49**, 258) has devised a binaural sound receiver by fitting the rubber tube to the ear pieces of the Shepherd type of stethoscope. The ear pieces are comfortably self-retaining as a result of the metallic spring that holds them in place. The author stresses the convenience and comfort of the arrangement, and mentions an added advantage in employing his both ears to listen to the sounds in the patient's ear, termining the contrivance an application of the stethoscope in a modified form to otologic use.

Meningococcic Mastoiditis.—Meningitis as a complication of acute aural infections is regarded as the common fatal outcome of such a disease, and when recognized all hope and treatment are abandoned. DIXON (*Arch. Otolaryngol.*, 1926, **3**, 151) reported a case which demonstrates the possibility of epidemic cerebrospinal meningitis as a complication of mastoiditis, and the subsequent lack of proper treatment owing to failure in recognizing the type of meningitis. About one month before observation by the author a boy, aged twelve years developed an earache on the right side. The ear was punctured by a

physician, with no relief. The following day another physician incised the tympanic membrane and removed the tonsils and adenoids. Within four days the parents noticed a stiffness of the neck and a tenderness over the right mastoid process. At the time of examination, some three weeks later, there was a leukocytosis (26,200) and a polycytosis (85 per cent). The spinal fluid was under increased pressure, turbid and showed 2700 polymorphonuclear leukocytes per cubic centimeter. No bacteria were found. As the right ear was still discharging and the mastoid tip tender, an exploratory mastoidectomy was performed. A badly infected mastoid was found and the dura of the middle fossa was acutely inflamed. Within forty-eight hours after operation the boy died. At autopsy a purulent basilar meningitis was found. Cultures from the spinal fluid and mastoid pus yielded Gram-negative intracellular diplococci, presumably meningococci.

Blastomycosis of the Larynx.—"Blastomycosis of the larynx is a rare disease, though probably not so rare as the paucity of literature on the subject would indicate." JACKSON (*Arch. Otolaryngol.*, 1926, **3**, 99) reported a case of apparently primary blastomycosis of the larynx in a man, aged forty-eight years, who was a clerk in a general store. Two years previously he developed a progressive hoarseness. He had been treated at different times and by different physicians for pulmonary and laryngeal tuberculosis and asthma; finally a tracheotomy was performed for the distressing dyspnea. A sensation of burning and "soreness" developed on the skin around the tracheotomic wound and to a less extent in the larynx and trachea. There was a slight cough and a small quantity of mucopurulent secretion was expelled from the cannula. Mirror laryngoscopy showed an infiltrative process involving the left side, part of the right side of the larynx and the intra-arytenoid space. The mass was grayish, granular below and whitish above, "as if brushed with silver nitrate." The left arytenoid was fixed and the arytenoid half of the epiglottic fold was swollen about twice the normal size. On the right side the cord was replaced by a nodular mass, extending from the anterior to the posterior commissure, the mass being covered with shining nodules having the appearance of frog spawn. In addition, direct laryngoscopy showed the entire right ventricular floor to be covered with whitish nodular excrescences, which extended out over the region where the cord should be and thence down into the trachea. Around the tracheotomic wound the rash presented three striking features: (1) A dark, intensely red, almost purplish color; (2) tiny nodules; (3) a sharp limitation of the external margin. Specimens from the larynx and margin of the tracheotomic wound were removed for histologic and bacteriologic examination. These were found to harbor blastomyces. Twenty drops of saturated aqueous solution of potassium iodid were then given thrice daily, and in five weeks the cutaneous nodules had disappeared and the laryngeal lesions were vanishing. The author analyzes 2 cases which had appeared previously in the literature. He concludes by saying that "The clinical and even the histologic resemblance of this disease to laryngeal tuberculosis would seem to urge the necessity of the exclusion of blastomycosis in every case of laryngeal tuberculosis in which tubercle bacilli are not found." The diagnosis cannot be made positively except by histologic examination.

RADIOLOGY

UNDER THE CHARGE OF

RUSSELL D. CARMAN, M.D.,

HEAD OF THE SECTION OF ROENTGENOLOGY, MAYO CLINIC, ROCHESTER, MINN.,

AND

CHARLES G. SUTHERLAND, M.B.,

ASSOCIATE IN SECTION OF ROENTGENOLOGY, MAYO CLINIC, ROCHESTER, MINN.

RUSSELL D. CARMAN.

Dr. Russell D. Carman died of cancer of the stomach on June 17, 1926. He had had charge of the Department of Roentgenology of this journal since its inauguration on February 26, 1925, and his death will be mourned by this staff, not only because of its personal loss of his unfailing courtesy and friendliness and ability in conducting the department, but also in its recognition of the passing of a master in his chosen field.

Dr. Carman was born at Iroquois, Ontario, March 18, 1875, but came to the United States in 1891 and was naturalized in 1897. He obtained his M.D. degree at the Marion Sims College of Medicine in 1901, and followed this by a year's postgraduate work at Johns Hopkins. After three years' general practice in St. Louis he specialized in roentgenology, and since 1913 has been head of the Section on Roentgenology of the Mayo Clinic. Last year he had the honor of being elected President of the American Roentgen Ray Society. He was a member of several American and foreign societies, and had written a book and numerous articles on his specialty. A sympathetic and vivid picture of the man appeared in the July number of the *American Journal of Roentgenology* (1926, **16**, 53), to which our readers are referred for further details. His death is a real loss to medical science.

The Editors.

The Roentgen Ray Diagnosis of Pedunculated Growths and Gastric Mucosa Prolapsing Through the Pylorus: Review of the Literature.—Pedunculated growths in the stomach exhibit certain Roentgen signs that should be of assistance in arriving at a correct diagnosis in the opinion of Eliason, Pendergrass and Wright (*Am. J. Roent. and Rad. Therap.*, 1926, **15**, 295). A fairly extensive review of the literature reveals 611 cases of benign gastric tumors, and of these 48 (7.5 per cent) were described as having a pedicle or being pedunculated. Their experience with the latter places the incidence at 20 per cent. In 48 cases papilloma, adenoma, fibroma and polyp were the most frequent, myoma next frequent and lipoma, cyst and angioma least frequent. The size of the lesions varied from about 15 to 0.5 cm. in diameter, and the location anywhere from the cardiac end of the stomach to the pylorus. A Roentgen ray examination was made on 10 of the 48 cases; a positive report was made in 9 cases. Moore first analyzed the Roentgen findings in benign tumors and detailed the diagnostic signs, but did not dwell particularly on the pedunculated

type. Five case reports are given in detail. They showed no definite and characteristic syndrome; the tentative diagnoses were duodenal ulcer, 2; gastric ulcer, 2; primary pernicious anemia, 1. Analysis of the Roentgen findings showed: (1) A central filling defect in the duodenal bulb surrounded by a thin shadow of bismuth. (2) This defect is not seen in films made in the erect posture, but only in those made in the prone posture, with some exceptions. (3) The whole may easily be overlooked in the roentgenoscopic examination. (4) There is no disturbance of peristalsis. (5) There is always a six-hour residue, the tumor having a ball-valve action. (6) There was no defect in the stomach in the pedunculated growths that prolapsed through the pyloric ring in their cases. (7) When prolapsed mucous membrane extends through the pyloric ring, the immediate 1 or 2 inches of the pyloric region of the stomach may show any one of three appearances: (*a*) Absence of bismuth with a large defect in the pyloric region, if a large amount of mucous membrane has prolapsed; (*b*) a less dense shadow if there is enough prolapsed mucous membrane to cause a thinning of the opaque meal; (*c*) an appearance of the rugæ of the stomach if the amount of mucous membrane is too small to cause the defect of (*a*) and too much to cause the defect of (*b*); the appearance of the (*c*) type of deformity is much the same as one gets when there is slight pressure of the pyloric region of the stomach on the spine. (8) With the patient in the right oblique horizontal position the pedunculated growth may more easily prolapse into the duodenum; this position is an important one in the roentgenoscopic examination. Because pedunculated growths and prolapsed mucous membrane are prone to undergo ulceration and subsequent bleeding, Roentgen ray study of the gastrointestinal tract should be a routine measure in cases of apparent pernicious anemia. The surgeon should always open and inspect the stomach when such growths are suspected, as these may be overlooked by the palpatory fingers.

Roentgen Examination of the Bronchi with Lipiodol.—LENK and HASLINGER (*Klin. Wchnschr.*, 1925, **32**, 1533). Filling of the bronchial tree with barium sulphate in oil to depict it was described in the American literature of 1920. Not until the French employed lipiodol, an oily solution of iodin, did the method come into extensive use. It is chiefly employed in examining for bronchiectasis. The writers do not spray the lipiodol into the trachea, as is usually done, but under fluoroscopic observation insert a catheter into the bronchus of the lobe which is to be examined and thus introduce the lipiodol. The following conclusions are offered: 1. In perfectly sound lungs, if the contrast medium reaches the alveoli the shadow flecks imitate those of saccular bronchiectasis. 2. Differentiation is possible only by screening; it is here superior to radiography. 3. Lipiodol in the bronchi will be coughed out in a few hours; that in the alveoli remains for months and disappears exclusively by resorption. The same mechanism may be assumed for the healing of pulmonary infiltrations. In the technic, alveolar filling should be avoided. 4. The contrast medium often accumulates, even against gravity, along the fissures, apparently because of the favorable relation between the lobar edges and the main bronchi. This fact explains the very common beginning of disease processes, notably pneumonia, in the edges of the lobes.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

FRANKLIN G. EBAUGH, M.D.,

PROFESSOR OF PSYCHIATRY AT UNIVERSITY OF COLORADO, DENVER, COLORADO,

AND

LLOYD H. ZIEGLER, M.D.,

ASSOCIATE IN PSYCHIATRY AT UNIVERSITY OF COLORADO, DENVER, COLORADO.

Gross Pontile Bleeding in Traumatic and Nontraumatic Cerebral Lesions.—WILSON and WINKELMAN (*Arch. Neurol. and Psychiat.*, 1926, **15**, 455) write that hemorrhage in the upper half of the pons is not uncommon, and when occurring vitiates to some extent localizing signs and symptoms. In each of the 13 cases presented an extrapontile lesion was present, being traumatic, vascular, neoplastic or, as in 1 case, abscess. Pontile hemorrhage was noted in 20 per cent of traumatic cases. There is a possibility that the socalled medullary edema may be the result of hemorrhage in the pons.

Influenza and Schizophrenia: An Analysis of Postinfluenzal "Dementia Precox," as of 1918, and Five Years Later.—MENNINGER (*Am. J. Psychiat.*, 1926, **5**, 469), in a study of 175 cases of postinfluenzal psychosis, found one-third in the acute phase, a schizophrenic syndrome. This psychosis occurred in individuals with or without evidence of hereditary taint or predisposition. Fifty cases have been followed for about five years. Of these, 35, or 70 per cent, have apparently undergone a cure and 10 per cent are improved. This would indicate that either the diagnosis or the older concept of dementia precox was wrong. The author thinks the latter to be the case.

Dementia Precox in Identical Twins.—PARKER (*J. Nerv. and Ment. Dis.*, 1926, **63**, 135) reviews briefly some of the literature on twins, and presents a brief history of twins with dementia precox described by Franz. These twins were about twenty-one years of age when they were both suffering from the disease, and they both first exhibited the disease a little over a year from each other. These twins were the last of 7 children born to the parents. The second case of twins having dementia precox was given to the author by Dr. E. Stanley Abbot, of McLean Hospital. These were girls. In 1 of these the characteristic signs of the disease were insidious from the sixteenth year of age, and she has been hospitalized continuously from about her twentieth year. A few months after she was hospitalized her sister suddenly became maniacal and suicidal and has been hospitalized ever since. These twins were the youngest of 3 children, whose father suffered a period with hypochondriacal and suicidal ideas. The twins described by Franz and Abbot were undoubtedly identical twins, that is, a product of a single egg. Because of the close biologic relationship of such twins, the fact that they both developed dementia precox argues in favor of

an inherent germinal defect—a theory propounded by many writers on the subject. The author points out that it would be extremely important as an argument against the germinal origin of dementia precox to find examples of 1 identical twin having dementia precox and the other not having it.

Vascular Lesions and Tumors of the Brain—Difficulties in Differential Diagnosis.—GLOBUS and STRAUSS (*Arch. Neurol. and Psychiat.*, 1926, **15**, 568). Differentiation between vascular lesions and tumors of the brain is at times exceedingly difficult as the symptoms of one condition often closely simulate those of the other. In vascular lesions below the tentorium, headache, vomiting and dizziness were the outstanding symptoms. These are probably due to the mild degree of internal hydrocephalus resulting from pressure on the fourth ventricle. In the cerebral vascular lesions, the ventricles were not affected, and the symptoms were those of early intellectual defects, emotional instability and paretic phenomena. From a study of 7 cases where the symptoms justified the diagnosis of brain tumor but in which the autopsy findings were those of vascular lesions, the authors have come to the conclusion that vascular lesions similating neoplasms of the brain can be subdivided as follows: (1) Cerebral lesions due to vascular damage secondarily acquired as the result of some generalized disease; (2) vascular lesions of the brain resulting from an inherent defect in the vascular system; (3) a transitional group in which the acquired and inherent factors are combined.

Neurologic Symptoms in Osteitis Deformans (Paget's Disease).—GREGG (*Arch. Neurol. and Psychiat.*, 1926, **15**, 613) states that osteitis deformans is not rare and believes that an early and definite diagnosis may be made by roentgenologic examination in 85 to 91 per cent of cases. This condition should always be ruled out in cases of unexplained fractures or neuralgias or nerve disabilities by roentgenologic examination. The neurologic symptoms which often appear before the stage of deformity are usually due to a disturbance of nerve function resulting from the proliferation of the bony structures involved.

The Action of Bulbocapnin in Three Cases of Paralysis Agitans and One Case of Tremor of Paralysis Agitans Type.—Of the 4 cases reported by DE JONG and HERMAN (*Arch. Neurol. and Psychiat.*, 1926, **16**, 55) 2 showed marked diminution of the tremor after treatment with 150 to 300 mg. of bulbocapnin, while 2 showed only doubtful improvement. Scopolamin was effective in 2 but without effect in the others. Bulbocapnin probably possesses the advantage of being nonhabit forming and is more constant in its effect.

General Paralysis Treated with Tryparsamid.—HASSIN and BASSOE (*Arch. Neurol. and Psychiat.*, 1926, **16**, 37) report a case of general paralysis treated intensively with neoarsphenamin and tryparsamid, which showed marked serologic and clinical improvement, although neither the degenerative phenomena nor the spirochetes were favorably affected. A cure of general paralysis either by tryparsamid or malaria cannot be expected.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,

AND

W. L. HOLMAN, M.D.,

ASSOCIATE PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

The Production of Experimental Endocarditis with Pneumococci and Streptococci in Immunized Animals.—It has often been noted that an endocarditis may occur in humans or animals following septicemias whether antibodies were present in the blood stream or not (Kinsella, 1917; Stone, 1923; Wright, 1925; Mair, 1923). Further experiments by WRIGHT (*J. Path. and Bact.*, 1926, **29**, 5) fail to determine the exact condition necessary for the production of the lesion, but they seem to show that repeated relatively innocuous doses of streptococci may result in the development of endocarditis. This may be because of some local factor resulting in a local failure of resistance. The septicemia is probably a secondary factor, and its occurrence in spite of marked bactericidal action and high antibody content of the blood is taken to mean that they are discharged from the lesion faster than they can be removed, rather than that they multiply in the blood stream. The author first worked with pneumococci and after immunizing the rabbits with autolyzed cultures to various degrees found that in some endocarditis or arthritis developed. One untreated animal died of acute septicemia, while some with well-developed immunity showed no effect. Further experiments showed that in previously immunized animals one could still produce endocarditis by gradually increasing doses of living pneumococci, though the exact modus operandi is not as yet evident. By repeated injections of nonhemolytic streptococci he was also able to produce endocarditis. All of these produced large amounts of agglutinins.

Experiments on the Influence of Fatigue on Infection.—BOYCOTT and PRICE-JONES (*J. Path. and Bact.*, 1926, **29**, 87) have attempted by experimental means to determine the correctness or not of the time-old adage "Resistance to infection is promoted by bodily rest." They used rats which were fatigued by being placed in 12-inch revolving drums made with a $\frac{1}{10}$-inch wire mesh covered by blanket material and revolved at 8 to 30 revolutions per minute. The animals were judged to be fatigued when they would lie on their backs and make no effort to stand. The only other objective measurement of fatigue was a lowering of the body temperature—rectal temperatures would fall from 100° to 90° or 85° F. The fall was roughly proportional to the degree of fatigue. A strain of Gaertner's bacillus, whose lethal dose was at least 0.2 cc. of a twenty-four-hour-broth culture injected

subcutaneously or intraperitoneally was used. Using a series of animals, one-half inoculated first and then fatigued, the other half fatigued first and then inoculated, the authors were unable to note any appreciable difference. Feeding experiments were then carried out, using large amounts of broth culture in bread, which is hardly ever fatal. Most of the fatigued animals showed obvious illnesses (diarrhea, cyanosis, etc.) and half of them died. In the controls none died, and only 1 seemed ill. In another experiment, using 36 rats, one-third of which were inoculated with bovine tubercle bacilli, one-third with human tubercle bacilli and the rest kept as controls, one-half of each group were fatigued fifteen times over a period of eight weeks. No evidence was obtained, however, that it was effective in breaking-down the natural resistance of the rat to tuberculosis. The experiments above, however, demonstrate that under certain circumstances fatigue promotes infection.

The Nature of the Movements of the Omentum.—Two theories have been held from time to time as to the causation of omental movement. The one favoring an intrinsic movement, the other passive movement. FLOREY, WALKER and CARLETON (*J. Path. and Bact.*, 1926, **29**, 97) report a series of experiments which led them to the conclusion that the omentum is totally incapable of any intrinsic movements. They cite the following factors, named in order of importance, as the chief agents bringing about omental movements: (1) Posture, (2) peristalsis of the gastrointestinal tract and (3) diaphragmatic movements. They carried out experiments on decerebrate cats and mice, injecting first inert materials and later bacteria. In some experiments celluloid windows were inserted in the abdominal wall, making it thus possible to observe the omentum under conditions closely akin to normal. Experiments carried out *in vitro* failed to demonstrate any signs of movement on the part of the omentum. The histologic reaction of the omentum to foreign bodies was also studied, and the reason for the rapid adhesion of foreign bodies to the omentum is given as due to the production of a layer of fibrin very rapidly and in large amounts. Thus its intrinsic powers seem to be limited to those of adhesion and encapsulation rather than of movement.

Lysis of Killed by Living Staphylococci.—In a recent review in these columns the work of TWORT (*Lancet*, 1925, ii, 642) on "The Transmissible Bacterial Lysis and its Action on Dead Bacteria" was synopsized. An earlier work was at that time overlooked. Gratia and Rhodes (*Comtp. rend. Soc. de biol.*, 1924, **90**, 640) observed the destruction of dead staphylococci in the presence of the socalled bacteriophage and living cocci. However, in the controls using a saline suspension of killed staphylococci minute amounts of living cocci digested the bodies of the dead cocci. Their studies showed that the living bacteria lived on the dead forms only when they were forced to by the absence of other nutrient material. This is not the phenomenon of transmissible bacterial lysis, but it would appear that the author in the work referred to did not appreciate this error in the interpretation of his results.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE, WASHINGTON, D. C.

An Epidemic of Scarlet Fever Spread by Ice Cream.—RAMSEY (*Am. J. Hyg.*, 1925, **5**, 668) reports an epidemic of scarlet fever which totaled 116 cases occurred in Flint, Michigan from July 25 to August 10, 1924, a time of year when the incidence of the disease is usually low. At the same time 9 cases were reported from Mt. Morris, and 3 cases from Goodrich, villages near Flint. Detailed epidemiologic investigation, by means of case histories and control histories on well persons, confirmed early suspicions and established the fact that the epidemic was spread by ice cream. Outbreaks of scarlet fever spread by this means are seldom mentioned in the literature. A filtrate prepared from a culture of hemolytic streptococci, isolated from the ice-cream maker, who caused the outbreak, gave typical reactions on individuals known to be Dick positive. The ice cream made by this man was eaten by 81.91 per cent of cases investigated, but comprised only 9.82 per cent of the total Flint supply. It was used by only 19.32 per cent of control individuals.

Further Contributions of Experimental Methods to the Study of Epidemics.—WEBSTER (*Am. J. Hyg.*, 1925, **5**, 335) considers what probably happens in the preëpidemic, the epidemic and the post-epidemic periods of an infectious disease. In the first place, three states of equilibrium of a population in respect to a given microbe may be recognized; it may be entirely free, it may harbor the more or less saprophytic variants of low virulence or it may contain, in addition to these saprophytic forms, scattered foci of infectious virulent types. Under any of these circumstances, an epidemic will be *preceded* by: (1) Either a widespread microbic dissociation or mutation of nonvirulent to virulent forms, or (2) a distribution of already existing virulent types throughout large areas. The first possibility, microbic dissociation, from nonvirulent to virulent, although conceivably possible, since the reverse process is known to occur has as yet little evidence for its support. Neufeld has divided infectious diseases into two categories; those which are caused by microörganisms capable of a saprophytic existence and others which are associated with bacteria of delicate parasitic requirements. In the first group he places tuberculosis, malaria, cholera and typhoid-like infections, and in the second, pneumonia, meningitis, streptococcus infections and so forth. He con-

siders microbic virulence in the second group to be unstable, which is probably true insofar as sudden postepidemic loss of virulence is concerned, but at present we must await further experimentation before deciding whether microbes suddenly and simultaneously assume a high degree of virulence in many communities or whether by hereditary or environmental influences affecting population susceptibility an originally virulent type suddenly is spread from some focus throughout a wide population area. In either event the epidemic is *incited* directly by a general and massive distribution of the virulent microbe throughout the community, and the morbidity or mortality curve, which results, is an expression of the resistance, hereditary and acquired, specific and nonspecific, of this population group to this dose of virulent microbes. Finally, after the epidemic wave has passed, when all available susceptible material is exhausted, the virulent microörganisms, finding no suitable nourishment, are reduced in numbers and tend to disassociate into nonvirulent types which are better suited to a saprophytic existence.

The Incidence of Mastoid Disease in the United States.—Blalock (*South. Med. J.*, 1925, **18**, 621) analyzed yearly reports from sixty-five hospitals in different parts of the country in order to find the geographic distribution of mastoid disease. Only figures from general hospitals, admitting all types of cases, have been used. Mastoid disease was found to be more than three times as common in the Northern, Midwestern and New England States as in the far Southern and far Western States. The cases of mastoid disease per 1000 admissions to hospitals were respectively 11.1, 7.4, 2.4 and 2.2. The Middle Atlantic States occupy an intermediary position (5.9). No conclusions can be drawn from the relative numbers of acute and chronic cases admitted. At least two-thirds of the cases admitted in all localities were of the acute type. The cause for the variation in mastoiditis in different localities is not clear.

Notice to Contributors.—Manuscripts intended for publication in the American Journal of the Medical Sciences, and correspondence, should be sent to the Editor, Dr. Edward B. Krumbhaar, Philadelphia General Hospital, 34th Street below Pine, Philadelphia, Pa.

Articles are accepted for publication in the American Journal of the Medical Sciences exclusively.

All manuscripts should be typewritten on one side of the paper only, and should be double spaced with liberal margins. Illustrations accompanying articles should be numbered and have captions bearing corresponding numbers. For identification they should also have the author's name written on the margin. The recommendations of the American Medical Association Style Book should be followed. It is important that references should be at the end of the article and should be complete, that is, author's name, title of article, journal, year, volume (in Arabic numbers) and page (beginning and ending).

Two hundred and fifty reprints are furnished gratis; additional reprints may be had in multiples of 250 at the expense of the author. They should be asked for when the galley proofs are returned.

Contributions in a foreign language, if found desirable for the Journal will be translated at its expense.